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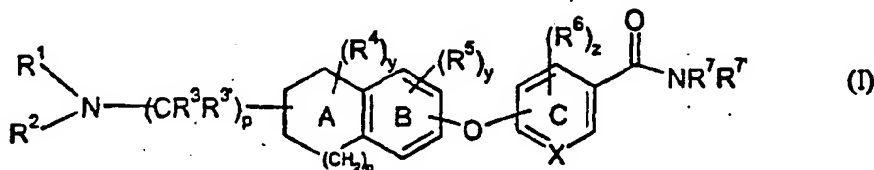
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(54) Title: 6-SUBSTITUTED NICOTINAMIDE DERIVATIVES AS OPIOID RECEPTOR ANTAGONISTS



(57) Abstract: A compound of the formula (I) or a pharmaceutically acceptable salt, enantiomer, racemate, diastereomers or mix-  
tures thereof, or a solvate thereof, formulations and methods of use thereof, as opioid receptor antagonists are disclosed wherein the  
variables are as described herein.



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## 6-SUBSTITUTED NICOTINAMIDE DERIVATIVES AS OPIOID RECEPTOR ANTAGONISTS

The present invention is in the field of medicinal chemistry. The invention relates specifically to compounds useful as opioid antagonists, methods of treatment, methods of using, and pharmaceutical compositions thereof.

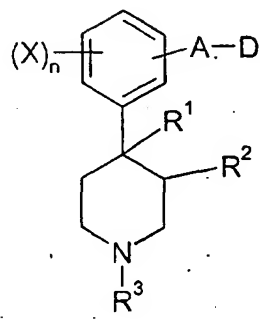
**Background:**

Three types of opioid receptors, mu, kappa, and delta opioid receptors are generally reported. Recent evidence points to the interactions between receptor dimer combinations of mu, kappa and/or delta receptors (called heterodimers) as also contributing to opioid activity. Opioid receptors and their normal regulation or lack thereof, has been implicated in disease states including irritable bowel syndrome, nausea, vomiting, pruritic dermatoses, depression, smoking and alcohol addiction, sexual dysfunction, stroke and trauma in animals. Therefore it is not surprising that the ability to antagonistically bind opioid receptors has been shown to produce ameliorative, preventative and/or treatment effects in animals including humans afflicted with one or more of these disease states.

More recently, antagonists of the opioid receptors have been found to increase metabolic energy consumption, and reduction of weight in obese rats while maintaining muscle mass. These findings indicate that an effective opioid antagonist may be useful in preventing, treating and or ameliorating the effect of obesity. Considering the percentage of the population that is obese in Western societies and the indirect costs associated with treating the effects and symptoms of obesity and Related Diseases, the impact of these findings cannot be overstated.

Though many opioid antagonists have been disclosed, the search continues for alternative and/or improved or more effective antagonists having an overall benefit to the patient with little or no major side effects. U.S Patent No. 4,891,379 discloses phenylpiperidine opioid antagonists useful for the treatment of diabetes and obesity. Clinical development of a compound claimed in U.S. Patent No. 4,191,771 was discontinued due to poor oral bioavailability characteristics. Bicyclic analogs of phenyl piperidine have been prepared and reported as opioid antagonists by Wentland, et al., Biorganic and Medicinal Chemistry Letters 11 (2001) 623-626; see also Wentland, et al., Biorganic and Medicinal Chemistry Letters 11 (2001) 1717-1721. Finally, European

Patent application number EP 1 072592A2 filed May 18, 2000, discloses phenylpiperidine compounds of formula I

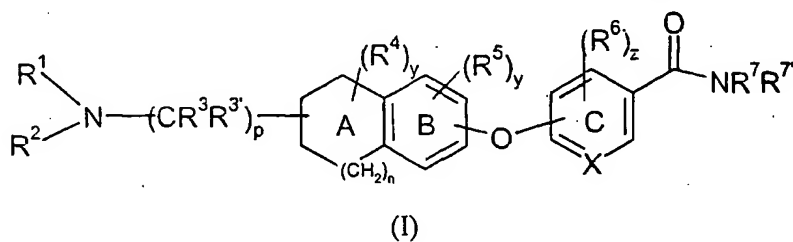


wherein A, D, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, X, and n have meanings given in the description, which are useful in the prophylaxis and in the treatment of diseases mediated by opioid receptors such as pruritus.

In spite of these and other disclosures of compounds useful as opioid receptor antagonists, there remains an unmet medical need for safe, effective and/or alternate treatment or prophylaxis of diseases associated with opioid receptors, particularly obesity and Related Diseases.

### SUMMARY OF THE INVENTION

The present invention provides a compound of the formula (I)



or a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer or a mixture thereof, wherein

X is C or N;

p is 0, 1, 2, or 3;

n is 0, 1, or 2;

R<sup>1</sup> and R<sup>2</sup> are independently selected from hydrogen, C<sub>1</sub>-C<sub>8</sub>alkyl, C<sub>2</sub>-C<sub>8</sub>alkenyl, C<sub>2</sub>-C<sub>8</sub>alkynyl, C<sub>1</sub>-C<sub>10</sub>alkylaryl, C<sub>4</sub>-C<sub>10</sub>alkylcycloalkane, C<sub>1</sub>-C<sub>8</sub>alkoxyalkyl, (CH<sub>2</sub>)<sub>n</sub>C(O)OR<sup>8</sup>, (CH<sub>2</sub>)<sub>n</sub>C(O)R<sup>8</sup>, (CH<sub>2</sub>)<sub>m</sub>C(O)NR<sup>8</sup>R<sup>8</sup>, and (CH<sub>2</sub>)<sub>m</sub>NSO<sub>2</sub>R<sup>8</sup>; wherein each of the alkyl,



alkenyl, and aryl groups are optionally substituted with one to five groups independently selected from C<sub>1</sub>-C<sub>8</sub>alkyl, C<sub>2</sub>-C<sub>8</sub>alkenyl, phenyl, C<sub>1</sub>-C<sub>8</sub>alkylaryl, and C<sub>4</sub>-C<sub>10</sub>alkylcycloalkane;; and wherein R<sup>1</sup> and R<sup>2</sup> may optionally combine with each other to form a 4, 5, 6, or 7-member nitrogen-containing heterocycle which nitrogen-containing heterocycle may further have substituents selected from the group consisting of oxo, amino, C<sub>1</sub>-C<sub>8</sub>alkyl, C<sub>2</sub>-C<sub>8</sub>alkenyl, C<sub>2</sub>-C<sub>8</sub>alkynyl, phenyl, C<sub>1</sub>-C<sub>8</sub>alkylaryl, C(O)C<sub>1</sub>-C<sub>8</sub>alkyl, CO(O)C<sub>1</sub>-C<sub>8</sub>alkyl, halo, C<sub>1</sub>-C<sub>8</sub>haloalkyl;

R<sup>3</sup> and R<sup>3'</sup> are each independently selected from Hydrogen, C<sub>1</sub>-C<sub>8</sub>alkyl, C<sub>2</sub>-C<sub>8</sub>alkenyl, C<sub>2</sub>-C<sub>8</sub>alkynyl, phenyl, aryl, and C<sub>1</sub>-C<sub>8</sub>alkylaryl;

R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> are each independently selected from C<sub>1</sub>-C<sub>8</sub>alkyl, C<sub>2</sub>-C<sub>8</sub>alkenyl, C<sub>2</sub>-C<sub>8</sub>alkynyl, C<sub>1</sub>-C<sub>8</sub>alkoxy, halo, C<sub>1</sub>-C<sub>8</sub>haloalkyl, phenyl, aryl, C<sub>1</sub>-C<sub>8</sub>alkylaryl, (CH<sub>2</sub>)<sub>m</sub>NSO<sub>2</sub>C<sub>1</sub>-C<sub>8</sub>alkyl, (CH<sub>2</sub>)<sub>m</sub>NSO<sub>2</sub>phenyl, (CH<sub>2</sub>)<sub>m</sub>NSO<sub>2</sub>aryl, -C(O)C<sub>1</sub>-C<sub>8</sub>alkyl, or -C(O)OC<sub>1</sub>-C<sub>8</sub>alkyl; wherein each R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> is attached to its respective ring only at carbon atoms, and wherein y is 0, 1, 2, or 3; and wherein z is 0, 1, 2, or 3

R<sup>7</sup> and R<sup>7'</sup> are each independently selected from hydrogen, C<sub>1</sub>-C<sub>8</sub>alkyl, C<sub>2</sub>-C<sub>8</sub>alkenyl, C<sub>2</sub>-C<sub>8</sub>alkynyl, C(O)C<sub>1</sub>-C<sub>8</sub>alkyl, hydroxy, C<sub>1</sub>-C<sub>8</sub>alkoxy, SO<sub>2</sub>C<sub>1</sub>-C<sub>8</sub>alkyl, SO<sub>2</sub>C<sub>1</sub>-C<sub>8</sub>alkylaryl, SO<sub>2</sub>C<sub>1</sub>-C<sub>8</sub>alkylheterocyclic, aryl, C<sub>1</sub>-C<sub>8</sub>alkylaryl, C<sub>3</sub>-C<sub>7</sub>cycloalkane, C<sub>1</sub>-C<sub>10</sub>alkylcycloalkane, (CH<sub>2</sub>)<sub>n</sub>C(O)OR<sup>8</sup>, (CH<sub>2</sub>)<sub>n</sub>C(O)R<sup>8</sup>, (CH<sub>2</sub>)<sub>m</sub>C(O)NR<sup>8</sup>R<sup>8</sup>, and (CH<sub>2</sub>)<sub>m</sub>NSO<sub>2</sub>R<sup>8</sup>; wherein the alkyl, alkenyl, and aryl groups are each optionally substituted with one to five groups independently selected from C<sub>1</sub>-C<sub>8</sub>alkyl, C<sub>2</sub>-C<sub>8</sub>alkenyl, phenyl, and C<sub>1</sub>-C<sub>8</sub>alkylaryl; and wherein R<sup>7</sup> and R<sup>7'</sup> may independently combine with each other, and with the nitrogen atom to which they are attached to form a 4, 5, 6, or 7-member nitrogen containing heterocycle which nitrogen containing heterocycle may further have substituents selected from the group consisting of oxo, amino, C<sub>1</sub>-C<sub>8</sub>alkyl, C<sub>2</sub>-C<sub>8</sub>alkenyl, C<sub>2</sub>-C<sub>8</sub>alkynyl, phenyl, C<sub>1</sub>-C<sub>8</sub>alkylaryl, C(O)C<sub>1</sub>-C<sub>8</sub>alkyl, CO(O)C<sub>1</sub>-C<sub>8</sub>alkyl, hydroxy, C<sub>1</sub>-C<sub>8</sub>alkoxy, halo, and haloalkyl;

R<sup>8</sup> is hydrogen, C<sub>1</sub>-C<sub>8</sub>alkyl, C<sub>2</sub>-C<sub>8</sub>alkenyl, C<sub>5</sub>-C<sub>8</sub>alkylaryl, (CH<sub>2</sub>)<sub>m</sub>NSO<sub>2</sub>C<sub>1</sub>-C<sub>8</sub>alkyl, (CH<sub>2</sub>)<sub>m</sub>NSO<sub>2</sub>Phenyl, (CH<sub>2</sub>)<sub>m</sub>NSO<sub>2</sub>aryl, -C(O)C<sub>1</sub>-C<sub>8</sub>alkyl, or -C(O)OC<sub>1</sub>-C<sub>8</sub>alkyl; and m is 1, 2.

The present invention also provides a method of using a compound of formula I for the prevention, treatment and/or amelioration of the symptoms of obesity and Related

Diseases comprising administering a therapeutically effective amount of a compound of formula I to a patient in need thereof.

The present invention also provides a pharmaceutical formulation comprising a compound of formula I in association with a carrier, diluent and/or excipient.

The present invention relates to the use of a compound of formula I for the treatment and/or prophylaxis of obesity and Related Diseases including eating disorders (bulimia, anorexia nervosa, etc.), diabetes, diabetic complications, diabetic retinopathy, sexual/reproductive disorders, depression, anxiety, epileptic seizure, hypertension, cerebral hemorrhage, congestive heart failure, sleeping disorders, atherosclerosis, rheumatoid arthritis, stroke, hyperlipidemia, hypertriglycemia, hyperglycemia, and hyperlipoproteinemia, substance abuse, drug overdose, compulsive behavior disorders (such as paw licking in dog), addictive behaviors such as gambling.

The present invention provides a compound of formula (I) useful for the manufacture of a medicament for the treatment, prevention and/or amelioration of symptoms associated with obesity and Related Diseases.

In another embodiment, the present invention provides a compound of formula I or a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer or a mixture thereof, useful as an appetite suppressant.

#### **Detailed Description of the Invention**

As used herein, the term "patient" includes human and non-human animals such as companion animals (dogs and cats and the like) and livestock animals.

The preferred patient or subject of treatment, amelioration and/or prevention of obesity and Related Diseases is a human.

The terms "treating" and "treat", as used herein, include their generally accepted meanings, *i.e.*, preventing, prohibiting, restraining, alleviating, ameliorating, slowing, stopping, or reversing the progression or severity of a pathological condition, or sequela thereof, described herein.

The terms "ameliorating" "preventing", "prevention of", "prophylaxis", "prophylactic" and "prevent" are used herein interchangeably and refer to reducing the severity of the symptoms associated with obesity and Related Diseases in a patient afflicted with same, or reducing the likelihood that the recipient of a compound of

formula I will incur or develop any of the pathological conditions, or sequela thereof, described herein.

As used herein, the term "effective amount" is synonymous with "effective dose" and means an amount of a compound of formula I that is sufficient in one or more administrations for preventing, ameliorating or treating a condition, or detrimental effects thereof, herein described, or an amount of a compound of formula I that is sufficient for antagonizing the opioid receptors to achieve the objectives of the invention.

The term "pharmaceutically acceptable" is used herein as an adjective and means substantially non-deleterious to the recipient patient.

The term "Active Ingredient" as used herein means a compound of formula I or a combination of compounds of formula I or a combination of a compound of formula I and a co-antagonist of the opioid receptor.

The term "formulation", as in pharmaceutical formulation, or "pharmaceutical composition" is intended to encompass a product comprising the Active Ingredient and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical formulations of the present invention encompass any effective composition made by admixing a compound of the present invention and a pharmaceutical carrier. The pharmaceutical formulations of the present invention also encompass a compound of the formula I and a pharmaceutically acceptable co-antagonist of the opioid receptors useful for the treatment and/or prevention of obesity and/or Related Diseases.

The term "Related Diseases" as used herein refers to such symptoms, diseases or conditions caused by, exacerbated by, induced by or adjunct to the condition of being obese. Such diseases, conditions and/or symptoms include but are not limited to eating disorders (bulimia, anorexia nervosa, etc.), diabetes, diabetic complications, diabetic retinopathy, sexual/reproductive disorders, depression (particularly that induced by the awareness and loss of self esteem associated with obesity), anxiety, epileptic seizure, hypertension, cerebral hemorrhage, congestive heart failure, sleeping disorders,

atherosclerosis, rheumatoid arthritis, stroke, hyperlipidemia, hypertriglyceremia, hyperglycemia, and hyperlipoproteinemia.

The term "suitable solvent" refers to any solvent, or mixture of solvents, inert to the ongoing reaction that sufficiently solubilizes the reactants to afford a medium within which the desired reaction is reasonably effected.

The term "mutual solvent" means a solvent that is used to dissolve sufficiently, two or more components of a reaction or mixture separately prior to reaction or mixing, that is a solvent common to more than one reagents or components of a mixture.

The term "nitrogen containing heterocycle" refers to a monocycle which is a 4, 5, 6, or 7-member ring containing 1, 2 or 3 nitrogen atoms in addition to the carbon atoms completing the ring size, or a combination of 1 nitrogen atom and 1, or 2 atoms selected from oxygen, and sulfur in addition to the appropriate number of carbon atoms completing the ring size. A nitrogen containing heterocycle as used here may have 0, 1 or 3 double bonds.

The term C<sub>1</sub>-C<sub>8</sub>alkyl refers to and includes all groups, structural isomers and /or homologues of alkyl groups having from 1 to 8 carbon atoms. When the term C<sub>1</sub>-C<sub>8</sub>alkyl precedes or prefixes another group, the term C<sub>1</sub>-C<sub>8</sub>alkyl, only limits the number of carbon atoms in the alkyl component. For example C<sub>1</sub>-C<sub>8</sub>alkylaryl means an aryl group having a C<sub>1</sub>-C<sub>8</sub>alkyl group substituent such that the number of carbon atoms in the group C<sub>1</sub>-C<sub>8</sub>alkylaryl is effectively the number of carbon atoms in the aryl group plus the number of carbon atoms in the C<sub>1</sub>-C<sub>8</sub>alkyl group. Similarly, the term C<sub>1</sub>-C<sub>8</sub>alkylcycloalkane, refers to a cycloalkane group having a C<sub>1</sub>-C<sub>8</sub>alkyl substituent, and wherein the entire group C<sub>1</sub>-C<sub>8</sub>alkylcycloalkane may itself be a substituent attached at either the alkyl group or the cycloalkyl group to a substrate.

The term "cycloalkane" means a cyclic alkyl group having from 3 to 8 carbon atoms i.e. from cyclopropane to cyclooctane unless otherwise indicated.

The term "halo" as used herein refers to a halogen including fluorine, chlorine, bromine or iodine.

As used herein the terms "alkenyl" refers to straight or branched carbon atoms having 1 or 2 carbon-carbon double bonds.

As used herein the terms "alkynyl" refers to straight or branched carbon atoms having 1 or 2 carbon-carbon triple bonds.

As used herein the term "alkoxy" refers to the group "O-alkyl" wherein alkyl is as indicated for the specific situation or as defined previously defined previously.

The term 'aryl' as used herein refers to compounds or groups having the Huckel  $4n+2$  pi electron arrangement and includes phenyl, benzyl, naphthyl, but excludes carbazoles.

As used herein, the term "protecting group" refers to a group useful for masking reactive sites in a molecule to enhance the reactivity of another group or allow reaction at another desired site or sites following which the protecting group may be removed. Protecting groups are usually used to protect or mask groups including but not limited to -OH, -NH, and -COOH.. Suitable protecting groups are known to one of skill in the art and are described in *Protecting groups in Organic Synthesis*, 3<sup>rd</sup> edition, Greene, T. W.; Wuts, P.G.M. Eds.; John Wiley and Sons, New York, 1999.

As used herein, the term "solvate" is a form of the compound of the invention wherein a crystal or crystals of a compound of the invention have been formed from a stoichiometric or non-stoichiometric amount of the compound of formula 1 and a solvent. Typical solvating solvents include for example, water, methanol, ethanol, acetone and dimethylformamide.

In those instances where a compound of the invention possesses acidic or basic functional groups, various salts may be formed which are more water soluble and/or more physiologically suitable than the parent compound. Representative pharmaceutically acceptable salts include but are not limited to the alkali and alkaline earth salts such as lithium, sodium, potassium, calcium, magnesium, aluminum and the like. Salts are conveniently prepared from the free acid by treating the acid in solution with a base or by exposing the acid to an ion-exchange resin.

Included within the definition of pharmaceutically acceptable salts are the relatively non-toxic, inorganic and organic base addition salts of compounds of the present invention, for example, ammonium, quaternary ammonium, and amine cations, derived from nitrogenous bases of sufficient basicity to form salts with the compounds of this invention (see, for example, S. M. Berge, *et al.*, "Pharmaceutical Salts," *J. Phar. Sci.*, 66: 1-19 (1977)). Moreover, the basic group(s) of the compound of the invention may be reacted with suitable organic or inorganic acids to form salts such as acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, hydrobromide,

camsylate, carbonate, chloride, clavulanate, citrate, chloride, edetate, edisylate, estolate, esylate, fluoride, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrochloride, hydroxynaphthoate, hydroiodide, isothionate, lactate, lactobionate, laurate, malate, malseate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, palmitate, pantothenate, phosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, tosylate, trifluoroacetate, trifluoromethane sulfonate, and valerate.

A compound of the invention as illustrated by formula I may occur as any one of its positional isomers, stereo chemical isomers or regioisomers, all of which are objects of the invention. Certain compounds of the invention may possess one or more chiral centers, and thus, may exist in optically active forms. Likewise, when the compounds contain an alkenyl or alkenylene group, there exist the possibility of cis- and trans-isomeric forms of the compounds. The R- and S- isomers and mixtures thereof, including racemic mixtures as well as mixtures of enantiomers or cis- and trans- isomers, are contemplated by this invention. Additional asymmetric carbon atoms can be present in a substituent group such as an alkyl group. All such isomers as well as the mixtures thereof are intended to be included in the invention. If a particular stereoisomer is desired, it can be prepared by methods well known in the art by using stereospecific reactions with starting materials which contain the asymmetric centers and are already resolved or, alternatively by methods which lead to mixtures of the stereoisomers and subsequent resolution by known methods. For example, a racemic mixture may be reacted with a single enantiomer of some other compound i.e. a chiral resolving agent. This changes the racemic form into a mixture of stereoisomers and diastereomers, because they have different melting points, different boiling points, and different solubilities and can be separated by conventional means, such as, for example, crystallization or chromatography.

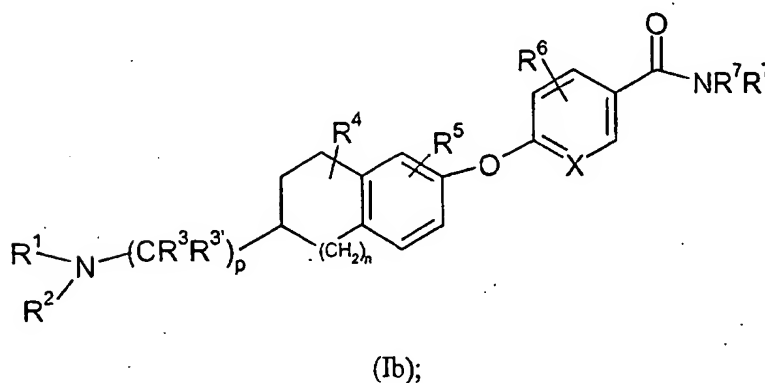
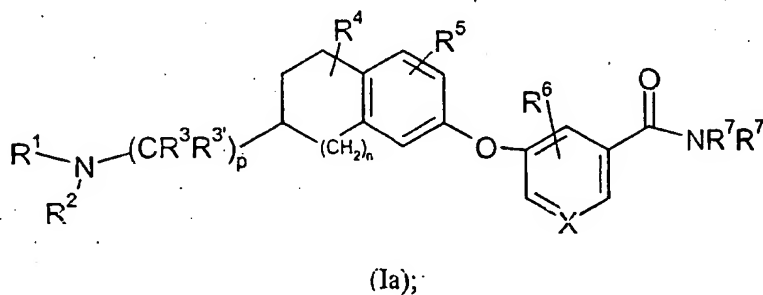
The compound(s) of the present invention have shown inhibition of orexigenic effects, and are thus useful as appetite suppressants either as a single therapy or in conjunction with exercise and/or other effective appetite suppressing or weight loss medications.

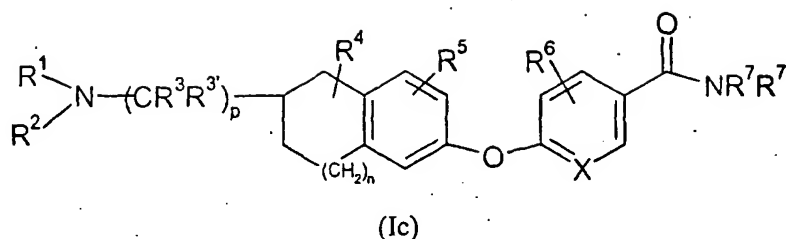
The efficacy of the compounds of the present invention has been shown by their activity in several biological activity models including an SPA GTP-gamma-S binding assay and other assays.

### Preferred Embodiments of the Invention

A compound of formula I preferably exists as a pharmaceutically acceptable salt. More preferred is the hydrochloride, or the bisulfate salt, or the oxalic acid salt of the compound of formula I.

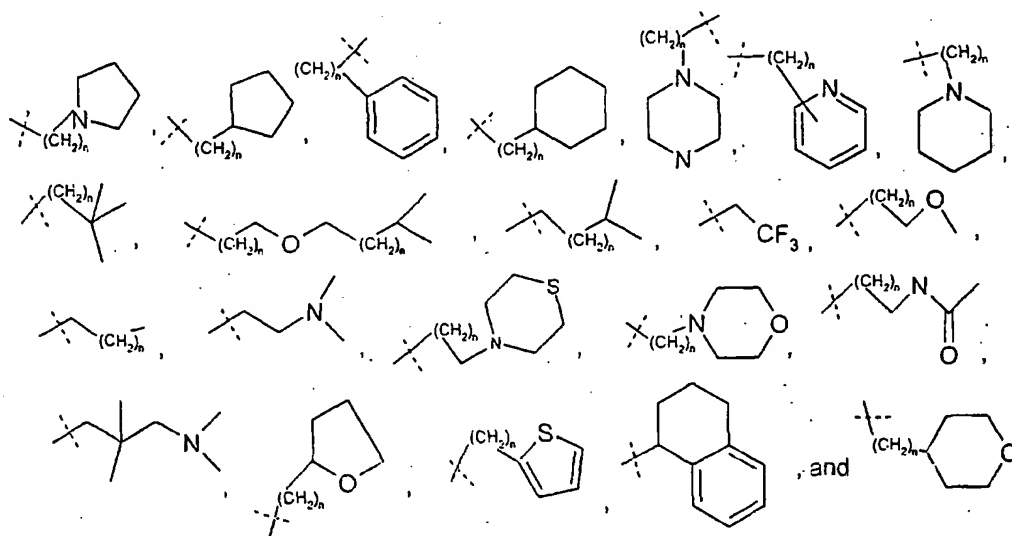
Though the groups  $R^4$ ,  $R^5$  and  $R^6$  may exist as multiple substituents on their respective ring substrates, a preferred embodiment of the invention involves compounds wherein each of  $R^4$ ,  $R^5$ , and  $R^6$  are absent, or are singly or doubly substituted on their respective ring substrates. Preferred embodiments of the compound of formula I include the substructures Ia, Ib and Ic as shown below:





For the groups  $R^1$  and  $R^2$

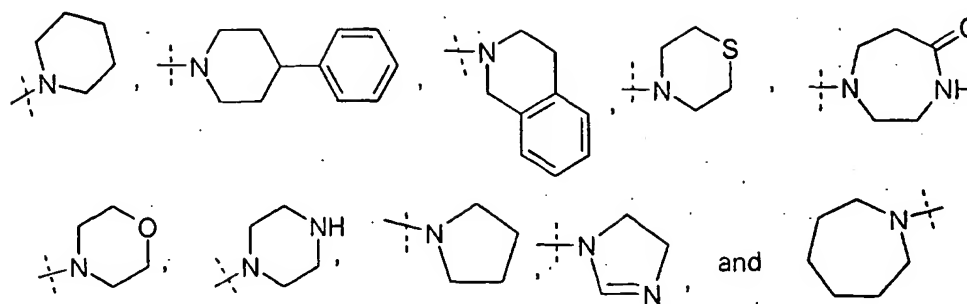
Preferred  $R^1$  and  $R^2$  groups are independently selected from the group consisting of Hydrogen, methyl, ethyl, propyl, pentyl, and isopropyl. Also preferred are  $R^1$  and  $R^2$  groups independently selected from the group consisting of:



each of which is optionally substituted with a group selected from the group consisting of halogen,  $C_1$ - $C_8$  alkyl,  $C_1$ - $C_8$  haloalkyl,  $C_1$ - $C_8$  thioalkyl,  $C_1$ - $C_8$  alkylamino, phenyl;  $C_1$ - $C_8$  alkylsubstituted phenyl,  $C_4$ - $C_8$  heterocycle or  $C_1$ - $C_4$  alkyl heterocycle; or combine with a group selected from  $C_1$ - $C_8$  alkyl, halogen,  $C_1$ - $C_8$  haloalkyl,  $C_1$ - $C_8$  thioalkyl,  $C_1$ - $C_8$  alkylamino, phenyl,  $C_1$ - $C_8$  alkylsubstituted phenyl,  $C_4$ - $C_8$  heterocycle or  $C_1$ - $C_4$  alkyl heterocycle to form a substituted or unsubstituted bicyclic.

Also preferred are  $R^1$  and  $R^2$  groups, which combine with each other and with the nitrogen to atom to which they are attached to form a group, selected from the group consisting of





each of which is optionally substituted with a group selected from the group consisting of halogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>1</sub>-C<sub>8</sub> haloalkyl, C<sub>1</sub>-C<sub>8</sub> thioalkyl, C<sub>1</sub>-C<sub>8</sub> alkylamino, phenyl, C<sub>1</sub>-C<sub>8</sub> alkylsubstituted phenyl, C<sub>4</sub>-C<sub>8</sub> heterocycle or C<sub>1</sub>-C<sub>4</sub> alkylheterocycle.

#### Preferred R<sup>3</sup> and R<sup>3'</sup> Groups

A preferred R<sup>3</sup> is Hydrogen. A preferred R<sup>3'</sup> group is selected from hydrogen, methyl, ethyl, propyl, isopropyl, phenyl and benzyl.

#### Preferred R<sup>4</sup> Groups

A preferred R<sup>4</sup> group is selected from the group consisting of halo, C<sub>1</sub>-C<sub>5</sub> alkyl, C<sub>1</sub>-C<sub>5</sub> haloalkyl, C<sub>1</sub>-C<sub>5</sub> alkoxy, C<sub>1</sub>-C<sub>5</sub> alkylamino, phenyl, C<sub>1</sub>-C<sub>5</sub> alkylphenyl, C<sub>1</sub>-C<sub>5</sub> alkylcycloalkyl, and C<sub>1</sub>-C<sub>5</sub> thioalkyl. More preferred is a R<sup>4</sup> group selected from the group consisting of methyl, ethyl, isopropyl, bromo, chloro, fluoro, trifluoromethyl, methoxy, ethoxy, thiomethyl, phenyl, and benzyl. A most preferred R<sup>4</sup> group is selected from the group consisting of methyl, ethyl, isopropyl, fluoro, chloro, bromo, trifluoromethyl, methoxy, ethoxy, propoxy, isopropoxy, and benzyl.

#### Preferred R<sup>5</sup> Groups

A preferred R<sup>5</sup> group is selected from the group consisting of halo, C<sub>1</sub>-C<sub>5</sub> alkyl, C<sub>1</sub>-C<sub>5</sub> haloalkyl, C<sub>1</sub>-C<sub>5</sub> alkoxy, C<sub>1</sub>-C<sub>5</sub> alkylamino, phenyl, C<sub>1</sub>-C<sub>5</sub> alkylphenyl, C<sub>1</sub>-C<sub>5</sub> alkylcycloalkyl, and C<sub>1</sub>-C<sub>5</sub> thioalkyl. More preferred is an R<sup>5</sup> group selected from the group consisting of methyl, ethyl, isopropyl, bromo, chloro, fluoro, trifluoromethyl, methoxy, ethoxy, thiomethyl, phenyl, and benzyl. A most preferred R<sup>5</sup> group is selected from the group consisting of methyl, ethyl, isopropyl, fluoro, bromo, chloro, trifluoromethyl, methoxy, ethoxy,

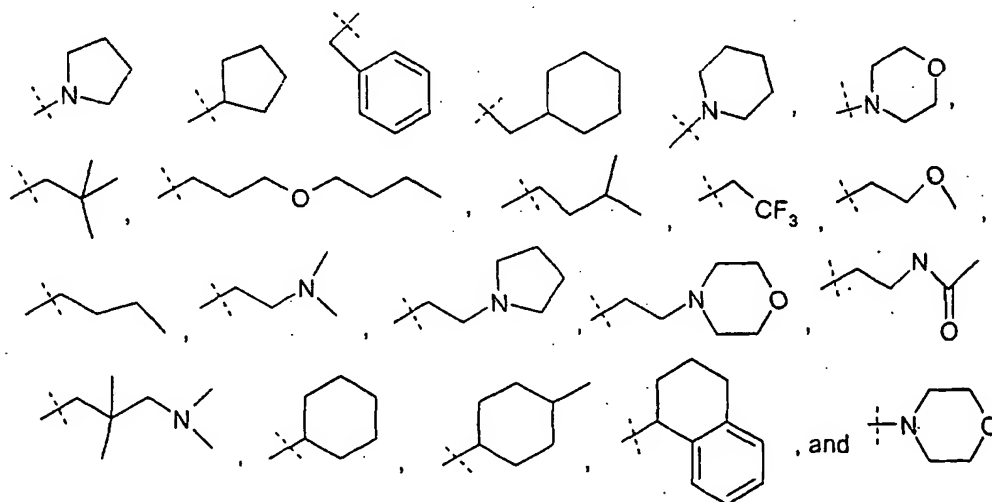
### Preferred R<sup>6</sup> Groups

A preferred R<sup>6</sup> group is selected from the group consisting of halo, C<sub>1</sub>-C<sub>5</sub> alkyl, C<sub>1</sub>-C<sub>5</sub> haloalkyl, C<sub>1</sub>-C<sub>5</sub> alkoxy, C<sub>1</sub>-C<sub>5</sub> alkylamino, phenyl, C<sub>1</sub>-C<sub>5</sub> alkylphenyl, C<sub>1</sub>-C<sub>5</sub> alkylcycloalkyl, and C<sub>1</sub>-C<sub>5</sub> thioalkyl. More preferred is an R<sup>6</sup> group selected from the group consisting of methyl, ethyl, isopropyl, bromo, chloro, fluoro, trifluoromethyl, methoxy, ethoxy, thiomethyl, phenyl, and benzyl. A most preferred R<sup>6</sup> group is selected from the group consisting of methyl, ethyl, isopropyl, fluoro, bromo, chloro, trifluoromethyl, methoxy, ethoxy, trifluoromethoxy, and benzyl.

Though the groups R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> may exist as multiple substituents on their respective ring substrates, a preferred embodiment of the invention involves compounds wherein each of R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> is absent, or is singly or doubly substituted on its respective ring substrate. In any event the requisite number of hydrogen atoms on the respective ring to satisfy valency requirements is implied.

### Preferred R<sup>7</sup> and R<sup>7'</sup> Groups

Preferred are R<sup>7</sup> and R<sup>7'</sup> groups independently selected from the group consisting of Hydrogen, methyl, ethyl, propyl, pentyl, isopropyl, phenyl and benzyl,



Most preferred R<sup>7</sup> and R<sup>7'</sup> are hydrogen atoms.

Preferred values for n and m, p, and z

A preferred value for n is 0, 1, or 2.

A preferred value for m is 1 or 2.

A preferred value for p is 0, 1, 2, or 3.

A preferred value for y or Z is 0, or 1 or 2.

Preferred A and C rings

A preferred A ring is cyclopentane, or cyclohexane. A preferred C ring is phenyl, or pyridine

Preferred compounds of the invention include but are not limited to compounds selected from the group consisting of

6-(8-Pentylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,

6-(5-Pentylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,

6-(5-Pentylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide,

6-(1-Pentylamino-indan-5-yloxy)-nicotinamide,

6-(1-Pentylamino-indan-4-yloxy)-nicotinamide,

6-(8-Benzylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,

6-(5-Benzylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,

6-(5-Benzylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide,

6-(1-Benzylamino-indan-4-yloxy)-nicotinamide,

6-(8-Phenethylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,

6-(5-Phenethylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,

6-(5-Phenethylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide,

6-(1-Phenethylamino-indan-4-yloxy)-nicotinamide,

6-{8-[2-(3-Fluoro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-  
nicotinamide,

6-{5-[2-(3-Fluoro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-  
nicotinamide,

6-{5-[2-(3-Fluoro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-1-yloxy}-  
nicotinamide,

6-{3-[2-(3-Fluoro-phenyl)-ethylamino]-indan-5-yloxy}-nicotinamide,

6-{1-[2-(3-Fluoro-phenyl)-ethylamino]-indan-5-yloxy}-nicotinamide,

6-{1-[2-(3-Fluoro-phenyl)-ethylamino]-indan-4-yloxy}-nicotinamide,

6-[8-(3-Methyl-butylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[5-(3-Methyl-butylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[5-(3-Methyl-butylamino)-5,6,7,8-tetrahydro-naphthalen-1-yloxy]-nicotinamide,

6-[8-(4-Methyl-cyclohexylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-  
nicotinamide,

6-[5-(4-Methyl-cyclohexylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-  
nicotinamide,

6-[5-(4-Methyl-cyclohexylamino)-5,6,7,8-tetrahydro-naphthalen-1-yloxy]-  
nicotinamide,

6-[1-(4-Methyl-cyclohexylamino)-indan-5-yloxy]-nicotinamide,

- 6-[1-(4-Methyl-cyclohexylamino)-indan-4-yloxy]-nicotinamide,
- 6-(7-Pentylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,
- 6-(6-Pentylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,
- 6-(6-Pentylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide,
- 6-(7-Pentylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide,
- 6-(7-Benzylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,
- 6-(6-Benzylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,
- 6-(6-Benzylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide,
- 6-(7-Benzylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide,
- 6-(7-Phenethylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,
- 6-(6-Phenethylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,
- 6-(6-Phenethylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide,
- 6-(7-Phenethylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide,
- 6-{7-[2-(3-Fluoro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-  
nicotinamide,
- 6-{6-[2-(3-Fluoro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-  
nicotinamide,

6-{6-[2-(3-Fluoro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-1-yloxy}-  
nicotinamide,

6-{7-[2-(3-Fluoro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-1-yloxy}-  
nicotinamide,

6-[7-(3-Methyl-butylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[6-(3-Methyl-butylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[6-(3-Methyl-butylamino)-5,6,7,8-tetrahydro-naphthalen-1-yloxy]-nicotinamide,

6-[7-(3-Methyl-butylamino)-5,6,7,8-tetrahydro-naphthalen-1-yloxy]-nicotinamide,

6-[7-(4-Methyl-cyclohexylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-  
nicotinamide,

6-[6-(4-Methyl-cyclohexylamino)-5,6,7,8-tetrahydro-naphthalen-1-yloxy]-  
nicotinamide,

6-[7-(4-Methyl-cyclohexylamino)-5,6,7,8-tetrahydro-naphthalen-1-yloxy]-  
nicotinamide,

6-[7-(3-Phenyl-propylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[6-(3-Phenyl-propylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[6-(3-Phenyl-propylamino)-5,6,7,8-tetrahydro-naphthalen-1-yloxy]-nicotinamide,

6-[7-(3-Phenyl-propylamino)-5,6,7,8-tetrahydro-naphthalen-1-yloxy]-nicotinamide,

6-[5-(2-Methylsulfanyl-ethylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-  
nicotinamide,

6-[1-(2-Methylsulfanyl-ethylamino)-indan-5-yloxy]-nicotinamide,

6-{5-[2-(3-Methoxy-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-  
nicotinamide,

6-{1-[2-(3-Methoxy-phenyl)-ethylamino]-indan-5-yloxy}-nicotinamide,

6-[5-(2-Dimethylamino-ethylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-  
nicotinamide,

6-[1-(2-Dimethylamino-ethylamino)-indan-5-yloxy]-nicotinamide,

6-[5-(2-Pyrrolidin-1-yl-ethylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-  
nicotinamide,

6-[1-(2-Pyrrolidin-1-yl-ethylamino)-indan-5-yloxy]-nicotinamide,

6-[5-(2-Pyridin-2-yl-ethylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-  
nicotinamide,

6-[1-(2-Pyridin-2-yl-ethylamino)-indan-5-yloxy]-nicotinamide,

6-[5-(2-Morpholin-4-yl-ethylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-  
nicotinamide,

6-[1-(2-Morpholin-4-yl-ethylamino)-indan-5-yloxy]-nicotinamide,

6-[1-(1,2-Diphenyl-ethylamino)-indan-5-yloxy]-nicotinamide,

6-{5-[2-(4-Fluoro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-  
nicotinamide,

6-{1-[2-(4-Fluoro-phenyl)-ethylamino]-indan-5-yloxy}-nicotinamide,

6-[5-(2-Acetyl-amino-ethylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-  
nicotinamide,

6-[1-(2-Acetyl-amino-ethylamino)-indan-5-yloxy]-nicotinamide,

6-{5-[2-(5-Fluoro-1H-indol-3-yl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-nicotinamide,

6-{1-[2-(5-Fluoro-1H-indol-3-yl)-ethylamino]-indan-5-yloxy}-nicotinamide,

3-[6-(5-Carbamoyl-pyridin-2-yloxy)-1,2,3,4-tetrahydro-naphthalen-1-ylamino]-propionic acid isopropyl ester,

3-[5-(5-Carbamoyl-pyridin-2-yloxy)-indan-1-ylamino]-propionic acid isopropyl ester,

6-(2-Pentylamino-indan-5-yloxy)-nicotinamide,

6-(2-Pentylamino-indan-4-yloxy)-nicotinamide,

6-(2-Benzylamino-indan-5-yloxy)-nicotinamide,

6-(2-Benzylamino-indan-4-yloxy)-nicotinamide,

6-[2-(3-Phenyl-propylamino)-indan-5-yloxy]-nicotinamide,

6-[2-(3-Phenyl-propylamino)-indan-4-yloxy]-nicotinamide,

6-[2-(3-Methyl-butylamino)-indan-5-yloxy]-nicotinamide,

6-[2-(3-Methyl-butylamino)-indan-4-yloxy]-nicotinamide,

6-[2-(2-Phenyl-propylamino)-indan-5-yloxy]-nicotinamide,

6-[2-(2-Phenyl-propylamino)-indan-4-yloxy]-nicotinamide,

6-(2-Phenethylamino-indan-5-yloxy)-nicotinamide,

6-(2-Phenethylamino-indan-4-yloxy)-nicotinamide,

6-{2-[(5-Fluoro-1H-indol-3-ylmethyl)-amino]-indan-5-yloxy}-nicotinamide,

6-{2-[(5-Fluoro-1H-indol-3-ylmethyl)-amino]-indan-4-yloxy}-nicotinamide,

6-[2-(3-Dimethylamino-2,2-dimethyl-propylamino)-indan-5-yloxy]-nicotinamide,

6-[2-(3-Dimethylamino-2,2-dimethyl-propylamino)-indan-4-yloxy]-nicotinamide,



6-{5-[(Benzo[b]thiophen-3-ylmethyl)-amino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-nicotinamide,

6-{1-[(Benzo[b]thiophen-3-ylmethyl)-amino]-indan-5-yloxy}-nicotinamide,

6-[5-(2-Methoxy-ethylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[1-(2-Methoxy-ethylamino)-indan-5-yloxy]-nicotinamide,

6-{5-[2-(3-Trifluoromethyl-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-nicotinamide,

6-{1-[2-(3-Trifluoromethyl-phenyl)-ethylamino]-indan-5-yloxy}-nicotinamide,

6-[5-(2-m-Tolyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-{5-[2-(4-Fluoro-phenyl)-1,1-dimethyl-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-nicotinamide,

6-{1-[2-(4-Fluoro-phenyl)-1,1-dimethyl-ethylamino]-indan-5-yloxy}-nicotinamide,

6-[5-(3-Hydroxy-propylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[1-(3-Hydroxy-propylamino)-indan-5-yloxy]-nicotinamide,

6-[5-(2,2,2-Trifluoro-ethylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[1-(2,2,2-Trifluoro-ethylamino)-indan-5-yloxy]-nicotinamide,

6-[5-(2,2-Diphenyl-ethylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[5-(4-Phenyl-piperidin-1-yl)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[1-(4-Phenyl-piperidin-1-yl)-indan-5-yloxy]-nicotinamide,

6-[5-(Benzyl-methyl-amino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[1-(Benzyl-methyl-amino)-indan-5-yloxy]-nicotinamide,

6-[5-(3,4-Dihydro-1H-isoquinolin-2-yl)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-  
nicotinamide,

6-[1-(3,4-Dihydro-1H-isoquinolin-2-yl)-indan-5-yloxy]-nicotinamide,

6-(5-Thiomorpholin-4-yl-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,

6-(1-Thiomorpholin-4-yl-indan-5-yloxy)-nicotinamide,

2-[6-(5-Carbamoyl-pyridin-2-yloxy)-1,2,3,4-tetrahydro-naphthalen-1-yl]-1,2,3,4-  
tetrahydro-isoquinoline-3-carboxylic acid tert-butylamide,

2-[6-(5-Carbamoyl-pyridin-2-yloxy)-1,2,3,4-tetrahydro-naphthalen-1-yl]-1,2,3,4-  
tetrahydro-isoquinoline-3-carboxylic acid tert-butylamide,

6-[5-(5-Oxo-[1,4]diazepan-1-yl)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-  
nicotinamide,

6-[1-(5-Oxo-[1,4]diazepan-1-yl)-indan-5-yloxy]-nicotinamide,

6-[5-(Methyl-phenethyl-amino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-  
nicotinamide,

6-[1-(3-Acetylamino-pyrrolidin-1-yl)-indan-5-yloxy]-nicotinamide,

6-[1-(3-Phenyl-piperidin-1-yl)-indan-5-yloxy]-nicotinamide,

6-[1-(3-Phenyl-pyrrolidin-1-yl)-indan-5-yloxy]-nicotinamide,

6-[1-(3-Propylamino-propylamino)-indan-5-yloxy]-nicotinamide,

6-[1-(3,3-Dimethyl-butylamino)-indan-5-yloxy]-nicotinamide,

6-(1-Decylamino-indan-5-yloxy)-nicotinamide,

6-[1-(2-Ethyl-hexylamino)-indan-5-yloxy]-nicotinamide,

6-{1-[(Tetrahydro-furan-2-ylmethyl)-amino]-indan-5-yloxy}-nicotinamide,

6-(1-Cycloheptylamino-indan-5-yloxy)-nicotinamide,

6-{1-[2-(1-Methyl-pyrrolidin-2-yl)-ethylamino]-indan-5-yloxy}-nicotinamide,

6-(1-Cyclopropylamino-indan-5-yloxy)-nicotinamide,

6-[1-(1,3-Dimethyl-butylamino)-indan-5-yloxy]-nicotinamide,

6-(1-Cyclooctylamino-indan-5-yloxy)-nicotinamide,

6-[1-(2,3-Dimethyl-cyclohexylamino)-indan-5-yloxy]-nicotinamide,

6-(1-Cyclobutylamino-indan-5-yloxy)-nicotinamide,

6-(1-Cyclopentylamino-indan-5-yloxy)-nicotinamide,

6-[1-(Cyclohexylmethyl-amino)-indan-5-yloxy]-nicotinamide,

6-{1-[(1-Ethyl-pyrrolidin-2-ylmethyl)-amino]-indan-5-yloxy}-nicotinamide,

6-[1-(3-Cyclohexylamino-propylamino)-indan-5-yloxy]-nicotinamide,

6-[1-(3-Methyl-cyclohexylamino)-indan-5-yloxy]-nicotinamide,

6-(1-Cyclohexylamino-indan-5-yloxy)-nicotinamide,

6-[1-(1-Isopropyl-2-methyl-propylamino)-indan-5-yloxy]-nicotinamide,

6-[1-(2-Cyclohex-1-enyl-ethylamino)-indan-5-yloxy]-nicotinamide,

6-[1-(2-Methyl-butylamino)-indan-5-yloxy]-nicotinamide,

6-[1-(4-Hydroxy-cyclohexylamino)-indan-5-yloxy]-nicotinamide,

6-[1-(1,4-Dimethyl-pentylamino)-indan-5-yloxy]-nicotinamide,

- 6-[1-(1-Cyclohexyl-ethylamino)-indan-5-yloxy]-nicotinamide,
- 6-[1-(3,3,5-Trimethyl-cyclohexylamino)-indan-5-yloxy]-nicotinamide,
- 6-[1-(2-Carbamoyl-cyclohexylamino)-indan-5-yloxy]-nicotinamide,
- 6-[1-(Cyclopropylmethyl-amino)-indan-5-yloxy]-nicotinamide,
- 6-[1-(3-Butoxy-propylamino)-indan-5-yloxy]-nicotinamide,
- 6-[1-(2,2,3,3,4,4,4-Heptafluoro-butylamino)-indan-5-yloxy]-nicotinamide,
- 6-{1-[3-(2-Oxo-pyrrolidin-1-yl)-propylamino]-indan-5-yloxy}-nicotinamide,
- 6-[1-(3-Azepan-1-yl-propylamino)-indan-5-yloxy]-nicotinamide,
- 6-[1-(2,2,3,3,3-Pentafluoro-propylamino)-indan-5-yloxy]-nicotinamide,
- 6-{1-[(2-Hydroxy-cyclooctylmethyl)-amino]-indan-5-yloxy}-nicotinamide,
- 6-[1-(Bicyclohexyl-2-ylamino)-indan-5-yloxy]-nicotinamide,
- 6-[1-(2-Hydroxy-cyclohexylamino)-indan-5-yloxy]-nicotinamide,
- 6-{1-[2-(2-Methyl-cyclohexyl)-ethylamino]-indan-5-yloxy}-nicotinamide,
- 6-{1-[2-(4-Methyl-cyclohexyl)-ethylamino]-indan-5-yloxy}-nicotinamide,
- 6-[1-(2-Cyclopentyl-ethylamino)-indan-5-yloxy]-nicotinamide,
- 6-[1-(Phenethylamino-methyl)-indan-5-yloxy]-nicotinamide,
- 6-[8-(Phenethylamino-methyl)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,
- 6-[3-(Phenethylamino-methyl)-indan-5-yloxy]-nicotinamide,

6-[5-(Phenethylamino-methyl)-5,6,7,8-tetrahydro-naphthalen-1-yloxy]-nicotinamide,

6-[1-(Benzylamino-methyl)-indan-5-yloxy]-nicotinamide,

6-[8-(Benzylamino-methyl)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[3-(Benzylamino-methyl)-indan-5-yloxy]-nicotinamide,

6-[5-(Benzylamino-methyl)-5,6,7,8-tetrahydro-naphthalen-1-yloxy]-nicotinamide,

6-{1-[(3-Methyl-butylamino)-methyl]-indan-5-yloxy}-nicotinamide,

6-{8-[(3-Methyl-butylamino)-methyl]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-  
nicotinamide,

6-{3-[(3-Methyl-butylamino)-methyl]-indan-5-yloxy}-nicotinamide,

6-{5-[(3-Methyl-butylamino)-methyl]-5,6,7,8-tetrahydro-naphthalen-1-yloxy}-  
nicotinamide,

6-{1-[(2-Cyclohexyl-ethylamino)-methyl]-indan-5-yloxy}-nicotinamide,

6-{8-[(2-Cyclohexyl-ethylamino)-methyl]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-  
nicotinamide,

6-{5-[(2-Cyclohexyl-ethylamino)-methyl]-5,6,7,8-tetrahydro-naphthalen-1-yloxy}-  
nicotinamide,

6-{1-[(Cyclohexylmethyl-amino)-methyl]-indan-5-yloxy}-nicotinamide,

6-{8-[(Cyclohexylmethyl-amino)-methyl]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-  
nicotinamide,

6-{3-[(Cyclohexylmethyl-amino)-methyl]-indan-5-yloxy}-nicotinamide,

6-{5-[(Cyclohexylmethyl-amino)-methyl]-5,6,7,8-tetrahydro-naphthalen-1-yloxy}-nicotinamide,

6-{1-[(2-Cyclopentyl-ethylamino)-methyl]-indan-5-yloxy}-nicotinamide,

and a pharmaceutically acceptable salt, solvate or enantiomer thereof.

Most preferred compounds of the invention include compounds selected from the group consisting of:

6-(8-Pentylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,

6-(5-Pentylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,

6-(5-Pentylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide,

6-(1-Pentylamino-indan-5-yloxy)-nicotinamide,

6-(1-Pentylamino-indan-4-yloxy)-nicotinamide,

6-(8-Benzylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,

6-(5-Benzylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,

6-(5-Benzylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide,

6-(1-Benzylamino-indan-4-yloxy)-nicotinamide,

6-(8-Phenethylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,

6-(5-Phenethylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,

6-(5-Phenethylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide,

6-(1-Phenethylamino-indan-4-yloxy)-nicotinamide,

6-{8-[2-(3-Fluoro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-nicotinamide, and a pharmaceutically acceptable salt, solvate or enantiomer thereof.

### Preparing the Compound of the Invention

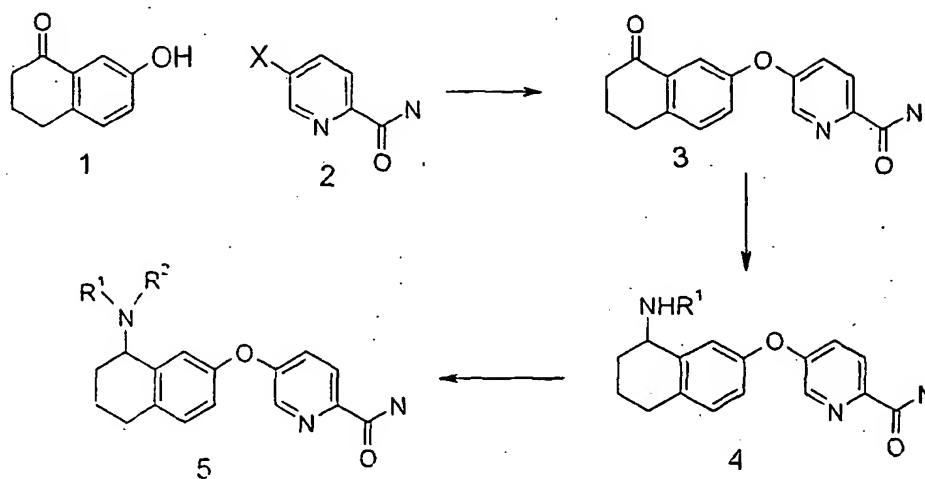
Compounds of formula I may be prepared as described in the following Schemes and Examples. The compounds employed as initial starting materials in the synthesis of compounds of the invention are well known and, to the extent not commercially available, are readily synthesized using specific references provided, or by standard procedures commonly employed by those of ordinary skill in the art and/or are found in general reference texts.

More particularly, the compounds of the invention are produced in accordance with schemes 1 through 10 that are described in detail below, or analogous methods thereto. These reactions are often carried out following known procedures, methods, or analogous methods thereto. Examples of such known procedures and methods include those described in general reference texts such as Comprehensive Organic Transformations, VCH Publishers Inc, 1989; Compendium of Organic Synthetic Methods, Volumes 1-10, 1974-2002, Wiley Interscience; Advanced Organic Chemistry, Reactions Mechanisms, and Structure, 5<sup>th</sup> Edition, Michael B. Smith and Jerry March, Wiley Interscience, 2001; Advanced Organic Chemistry, 4<sup>th</sup> Edition, Part B, Reactions and Synthesis, Francis A. Carey and Richard J. Sundberg, Kluwer Academic / Plenum Publishers, 2000, etc., and references cited therein.

Compounds of the present invention are generally prepared starting with a coupling reaction to form the ether linkage between the aryl groups Ar<sup>2</sup> and Ar<sup>3</sup>. The alkylamino appendage or substituent on the bicyclic ring Ar<sup>2</sup> is formed by reductive amination on a keto functionality already present on the ring followed by elaboration of the substituent to form the desired group. The final compound is then obtained by elaboration of a cyano or amido group on the ring Ar<sup>3</sup>. Alternatively the side chain on Ar<sup>2</sup> is formed by displacement of an alkylhalide substituent on the Ar<sup>2</sup> ring. The

alkylhalide substituent is itself introduced via a hydroxy group or a reduced keto group. Details of specific procedures are provided in the schemes below.

Scheme 1



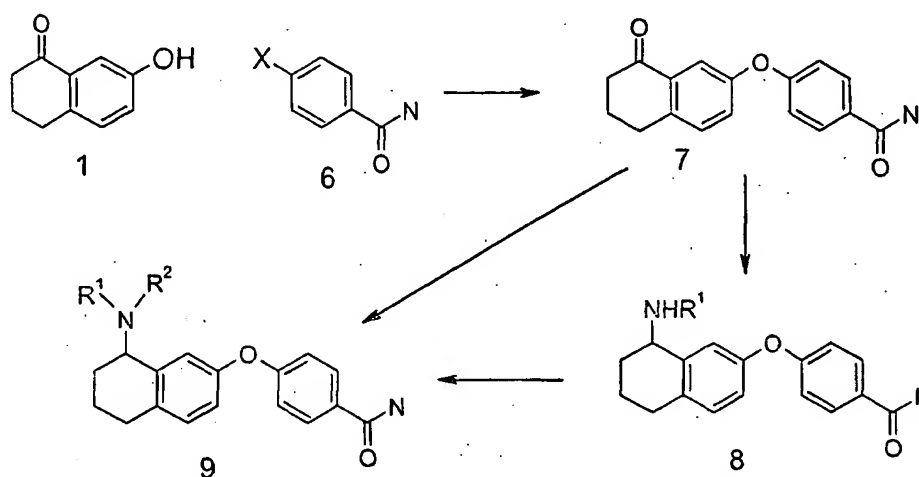
As shown in scheme 1, certain compounds of the present invention are prepared starting with an optionally substituted hydroxytetralone compound 1. The tetralone compound provides the framework for the 6,6-bicyclic structure representing  $Ar^2$  of formula 1. The hydroxytetralone 1 is typically reacted with a halonicotinonitrile compound or a halonicotinamide 2 to afford the ether linked compound 3. Various positional isomers of hydroxytetralone, halonicotinonitrile or halonicotinamide may be employed to effect preparation of position isomers or analogs of the compound 3. Preferred halogen substituents for the displacement reaction are fluoro, chloro, or bromo. The displacement reaction is preferably performed under basic conditions such as with sodium or potassium carbonate in a suitable polar solvent such as for example, dimethylacetamide (DMA), dimethylformamide (DMF), dimethyl sulfoxide (DMSO) and the like. The reaction is typically performed at temperatures ranging from room temperature to reflux temperatures depending on the particular substrates. The ether 3 is then reductively aminated with a suitable amine to form the compound 4 or 5. The use of a primary amine results in the amine 4, which may be further converted to the tertiary amine 5 using processes known to one of skill in the art and/or disclosed in the experimental section. Alternatively, where a tertiary amine is desired and the reaction is



not likely to be detrimentally affected by steric considerations, a secondary amine may be used in the reductive amination step to afford the compound 5 or analog thereof.

Preparing the benzamide analog of the compounds of formula 4 or 5 may be accomplished by using the appropriately substituted benzamide or benzonitrile as shown in scheme 2 below.

Scheme 2

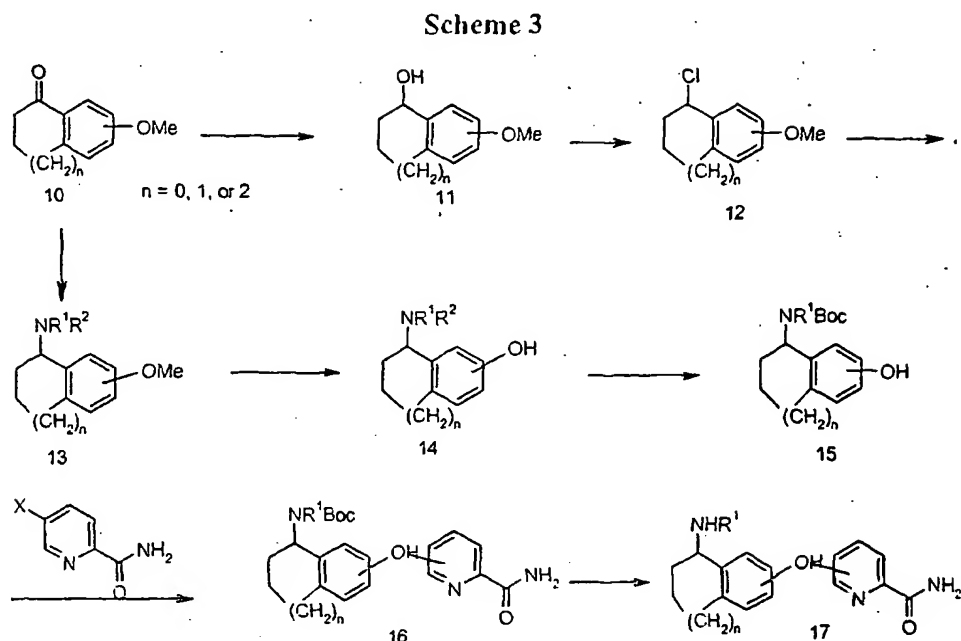


For Schemes 1 and 2, wherein the C-ring of formula I is introduced via the nitrile, the resulting nitrile may be converted to the amide by basic hydrolysis in the presence of hydrogen peroxide. Details of this and other methods of hydrolyzing nitrile to amide are known to one of skill in the art and/or are disclosed in the experimental section. Where the nitrile is used in the initial reaction, it may be preferable for some substrates that the conversion to the amide be effected prior to the reductive amination step. As in Scheme 1,

The indane analog (wherein the A-ring is a 5-member ring) of compounds of formula I may be similarly prepared using the desired 2-hydroxy indanone as starting material in a scheme such as Scheme 2 above. As with Scheme 1, the coupled product 7 is then reductively aminated with ammonia or a desired substituted amine to afford the compound 8 or 9 directly.

Compounds of formula I wherein the appropriately substituted hydroxytetralone or hydroxyindanone or hydroxy tetrahydroisoquinolone is not commercially available

may be accessed starting from the corresponding methoxy compound 10 as shown in Scheme 3.

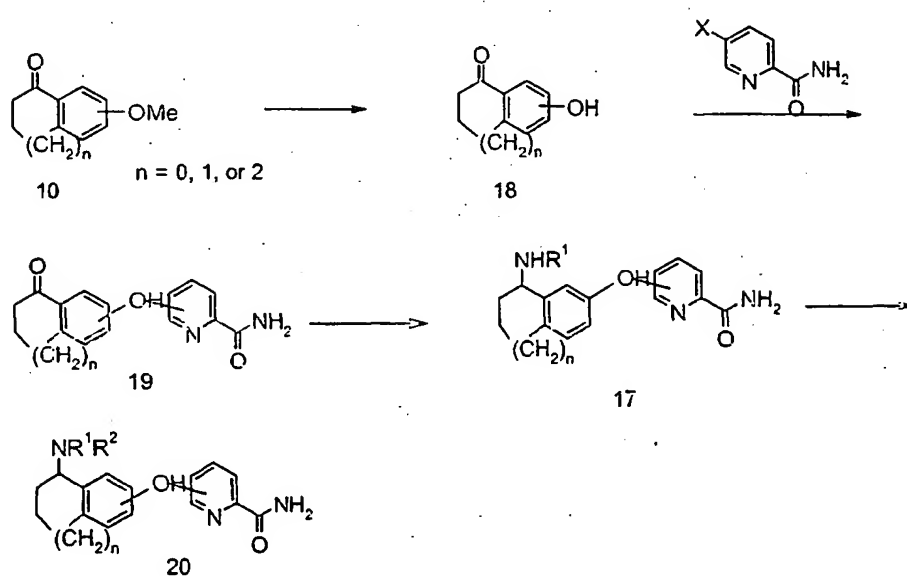


Protection of the hydroxy group as the methoxy group as in compound 10 also allows for installation of the amino side chain on the bicyclic ring via a displacement reaction of an intermediate halide. As shown in Scheme 3, the tetralone or indanone compound 10 is reduced to the alcohol 11 using known reducing agents such as the borohydride reagents e.g. sodium borohydride, or the aluminum hydride reducing agents, e.g.  $\text{NaAlH}_4$ . The procedures and conditions for effecting such reductions are known to one of skill in the art, may be found in general organic reference texts disclosed herein or are disclosed in the experimental section. The alcohol 11 is then displaced with a nucleophile source to afford a leaving group such as for example, chloride or bromide or other sulfonate ester. Formation of chloride leaving group for example, is accomplished by reacting the intermediate 11 with for example, thionyl chloride in a suitable solvent such as toluene or dichloromethane at temperatures ranging from ambient to reflux temperatures. The resulting chloride 12 is displaced with an amine in a suitable polar aprotic solvent to afford either the primary, secondary or tertiary amine depending on whether the reacting amine source is ammonia, primary or secondary amine. The reactive hydrogen of a primary or secondary amine 13 (where one or both of  $\text{R}^1$  and  $\text{R}^2$  are

hydrogen) may be protected as the Boc- group after de-methylation to form compound 15. Compound 15 may be reacted with a source of nicotinamide or nicotinonitrile or benzamide or benzonitrile as desired. The use of optionally substituted 3-halonicotinamide is shown in the Scheme 3. One of skill in the art is aware that other sources of the Ar<sup>3</sup> group according to formula I may be introduced as discussed herein or as disclosed in the experimental section.

A modification of the scheme 3 protocol wherein the coupling to form the ether backbone of a compound of formula I is effected prior to formation of the amino side chain is shown in scheme 4 below.

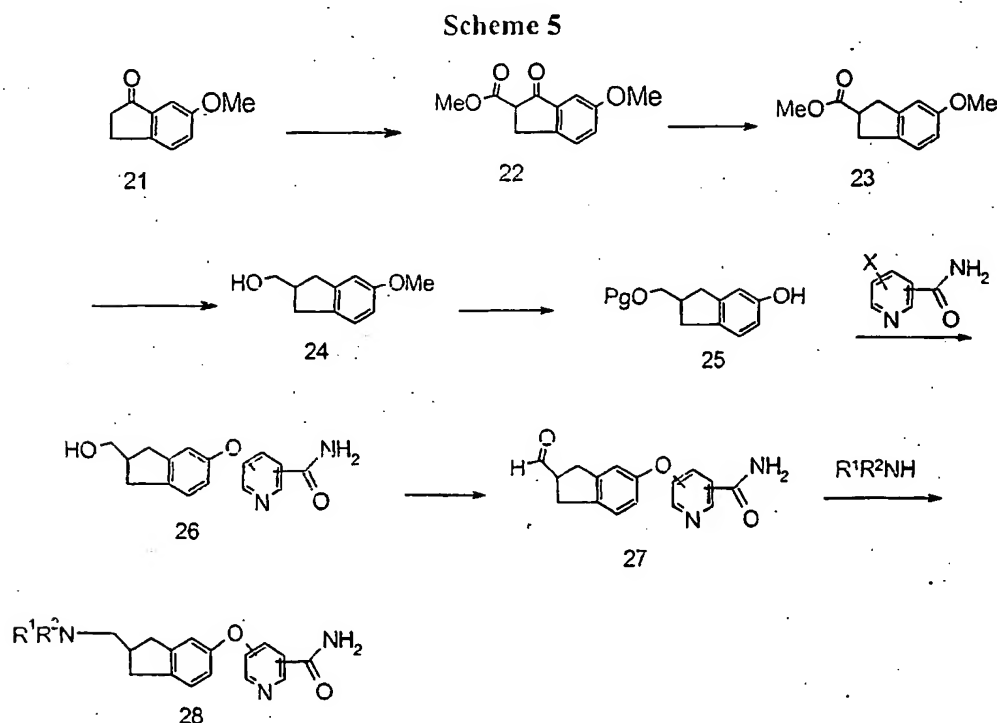
Scheme 4



According to Scheme 4, the starting material 10 is de-methylated to afford the hydroxy compound 18. The de-methylation may be accomplished by use of 48% HBr or boron tribromide. Details of the procedures for effecting the above de-methylation has been discussed previously, are known to one of skill in the art and/or disclosed in the experimental section herein. The hydroxy compound 18 is then coupled with a benzamide or nicotinonitrile or other source of the C-ring of a compound of formula I. The use of halonicotinonitrile is shown in the scheme above to afford the ether compound

19. The conditions to effect the coupling reaction have been described earlier and in the experimental section. The ether 19 is reductively aminated at the carbonyl group to afford the amine compound 17. The amine 17 may be converted to the compound 20 wherein both  $R^1$  and  $R^2$  are not hydrogen atoms following procedures known to one of skill in the art.

Compounds of formula I, wherein the alkyl chain length of the amino side chain i.e.  $p$  is 1, may be prepared following the protocol of Scheme 5 below or known variations thereof.

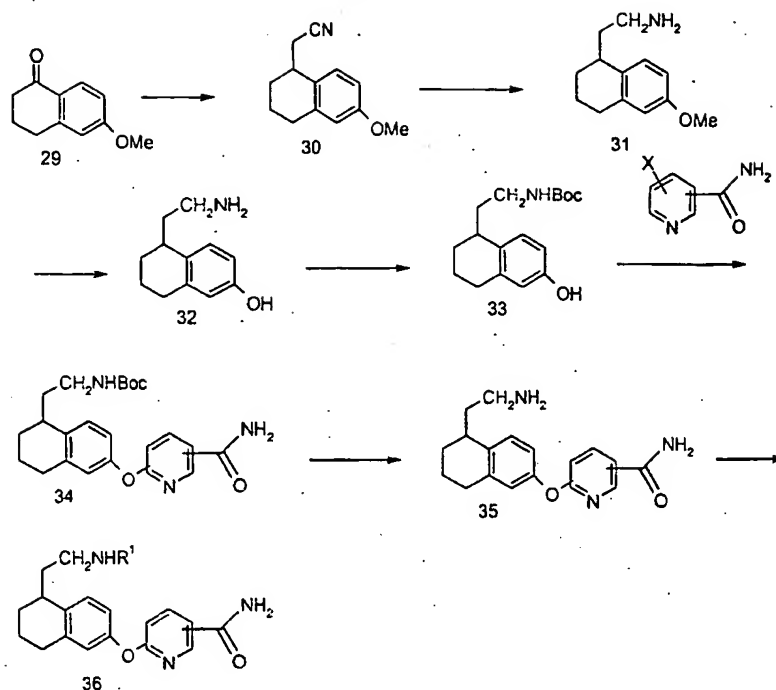


As shown in Scheme 5, 5-methoxyindanone (21) may be reacted with dimethylcarbonate in the presence of a strong base such as sodium hydride to afford the 5-methoxyindan-1-oxo-2-carboxylic acid methyl ester (22). The indanone ester 22 may be reduced to the indane methyl ester 23 using palladium on carbon in the presence of a proton donor such as perchloric acid, and a suitable solvent such as acetic acid. The resulting indane methylester 23 is further reduced to the methoxyindane alcohol 24 using

lithium aluminum hydride or other suitable reducing agents. The free hydroxy group of compound 24 may be protected using suitable OH-protecting groups prior to demethylation reaction of 24 to afford the product 25. The removal of the methoxy group of the protected methoxyindane alcohol 24 may be accomplished using concentrated HBr, e.g. 48% HBr. Alternatively, boron tribromide may be used. The resulting hydroxy compound 25 is then coupled with a source of nicotinonitrile, nicotinamide, benzonitrile or benzamide. A suitable source in each case is an appropriately substituted halide. Scheme 5, for example shows the use of a halonicotinamide. A preferred halogen is the chloride. The coupling reaction to form the ether linkage has been described previously, and affords the ether 26 following deprotection as appropriate. Oxidation of the alcoholic functionality of the ether 26 affords the aldehyde 27. Specific procedures for oxidation of the alcohol include the Swern oxidation. The Swern oxidation may be accomplished by adding the alcohol 26 into a cold solution/mixture formed by adding dimethyl sulfoxide to a solution of oxalyl chloride in a suitable solvent such as dichloromethane. Detailed procedures for effecting the Swern oxidation and other methods of oxidizing alcohols are provided in general reference texts, are known to one of skill in the art, and/or disclosed in the experimental section herein. The aldehyde 27 is then reductively aminated with the desired amine to afford the compound 28.

Compounds of formula I wherein p is 2 may be prepared by the procedure given in schemes 7 or 8 below or analogous procedures obtained by modifications known to one of skill in the art.

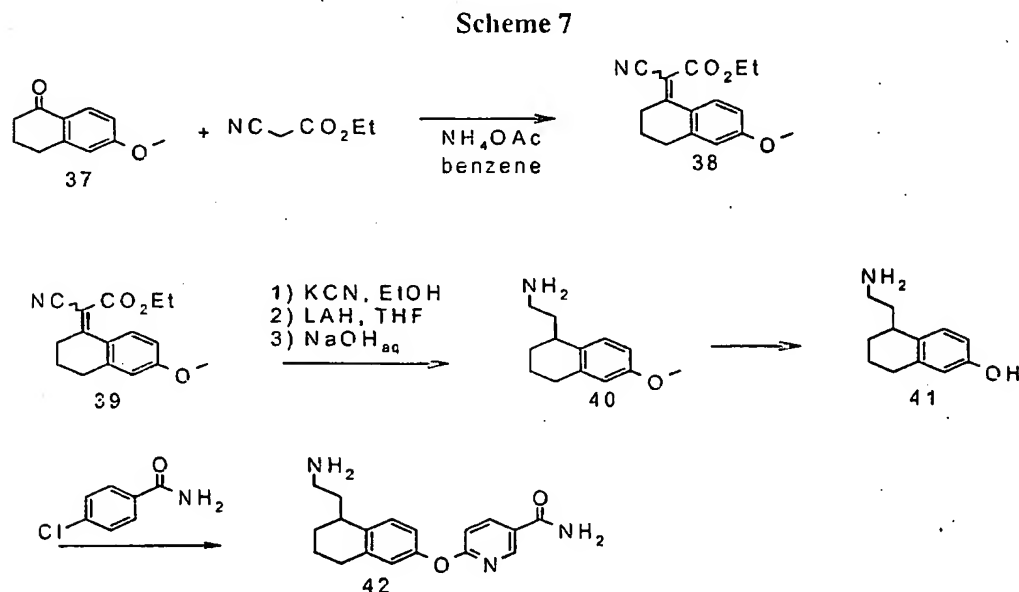
Scheme 6



Compound 29 of Scheme 6 may be converted to compound 30 via a series of reactions beginning with formation of an acrylonitrile via the Horner-Emmons-Wadsworth modification of the Wittig reaction using diethylphosphonoacetonitrile diethylcyanomethyl phosphonate to form an acrylonitrile intermediate (see *J. Org. Chem.* 30, 505 (1965) and also *J. Am. Chem. Soc.*, 83 1733 (1961)). The acrylonitrile intermediate or substituted derivative thereof, may be reduced to the saturated nitrile 30 using for example hydrogenation using palladium (II) chloride catalyst, and sodium borohydride in a protic solvent such as methanol. For reference see Jelliman, C., et al, *J. Med. Chem.*, 43 (22) 4051-4062 (2000). The nitrile 30 may be reduced to the ethylamine derivative 31 by hydrogenation using Raney Nickel and ammonium hydroxide in THF as disclosed in Jelliman et. al., *supra*. The ethylamine compound 31 may be demethylated to form the hydroxy compound 32. The hydroxy compound 32 may be reacted directly with a nicotinamide source or a benzamide source or synthon to afford a compound of the invention. Alternatively the hydroxy compound 32 is protected at the amine prior to coupling with a nicotinamide or benzamide source or synthon. The protected compound 33 is coupled with a source of the 'C' ring to afford the coupled and protected compound

34. The compound 34 is then de-protected to afford the desired compound of the invention 35 which may itself be converted to other substituted amine derivatives such as compound 36 following procedures known to one of skill in the art or disclosed herein. One of skill in the art is aware that compounds of formula I wherein  $R^3$  and/or  $R^{3'}$  are other than hydrogen may be prepared by alkylation at the free methyne carbon atom of the acrylonitrile intermediate from compound 29, or the nitrile 30 to afford substituted derivatives of a compound of formula I. Such alkylations may be accomplished by following procedures similar to those disclosed in *Synthesis*, 516 (1975).

In an alternate method, compounds of formula I wherein p is 2 may be prepared following a scheme such as Scheme 7.

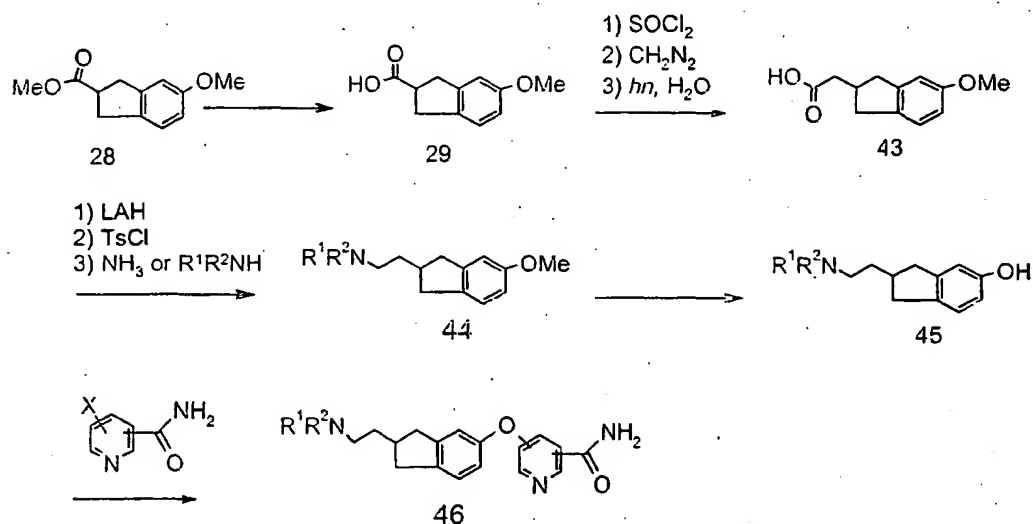


As shown in Scheme 7, methoxy tetralone 37 is subjected to a Knoevenagel type nucleophilic substitution with ethylcyanoacetate to afford upon elimination of water, the acrylonitrile acetate compound 38 according to procedures described in Mukhopadhyay et al. *J. Chem Res, Synop* 1993, 12, 476-477. Other examples of the Knoevenagel reaction may be found in *Name Reactions and Reagents in Organic Synthesis* by Bradford P. Mundy and Michael G. Ellerd, Wiley InterScience Publishers, 1988, New York, New York and references cited therein. The compound 38 is then subjected to a decarboxylation and reduction sequence to afford the aminoethyl compound 40 according

to a procedure similar to that described in *New et al., Synthesis* 1983, 388. The resulting 4-methoxy aminoethyl compound 40 is then demethylated to afford the hydroxy compound 41 using, for example, boron tribromide or 48% HBr as the demethylating agent. The hydroxy compound 41 is then reacted with an appropriately substituted halo nicotinamide or halo-benzamide source (e.g. 4-chlorobenzene carboxamide shown) or synthon thereof, to afford the ether compound 42. The ether compound 42 may be elaborated to substituted amines by procedures known to one of skill in the art.

In yet an alternative procedure compounds of formula I wherein p is 2 may be prepared following a scheme such as Scheme 8.

Scheme 8

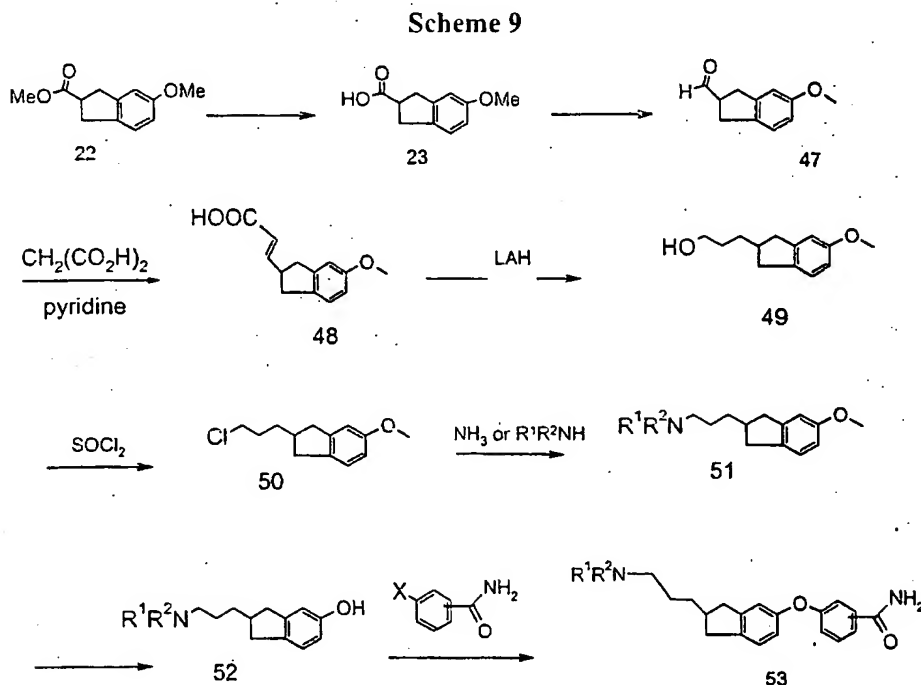


According to Scheme 8, compound 28 (Scheme 5) may be hydrolyzed to the acid 29. The acid 29 is further converted to an acid halide intermediate, e.g. acyl chloride, using for example, thionyl chloride in an aprotic solvent. The acyl halide intermediate is then converted to a diazoketone intermediate by reaction with diazomethane. The diazoketone intermediate is converted to a methylester intermediate which upon a Arndt-Eistert reaction affords the acid 43. Procedures for converting the acid 29 to the acid 43 are similar to those employed and disclosed in Walsh, E. J., et al, *Tetrahedron Letters*, 1986, (27) 1127-1130 and references therein. The acid 43 is then reduced to the alcohol



using, for example, lithium aluminum hydride. The intermediate alcohol is converted to a chloride intermediate by reaction with thionyl chloride or other chlorinating agent. The chloride intermediate is displaced with ammonia or amine to afford the primary or substituted amine **44** respectively. The methoxy amine compound **44** is then demethylated at the methoxy group to form the alcohol **45**. The alcohol **45** is then coupled with an appropriately substituted halonicotinamide, halo-benzamide or other desired heterocyclic amide source or synthon to afford compound **46**, a compound of the invention.

Compounds of formula I wherein p for the amine side chain is 3 may be prepared as shown in scheme 9.



As shown in scheme 9, compound **22** which formation has been discussed previously, may be converted to the acid **23** by basic hydrolysis followed by acidic workup. The acid **23** may be reduced to the aldehyde **47**. Procedures for reduction of acids to aldehydes are known to one of skill in the art. The aldehyde **47** is then reacted with malonic acid in the presence of a base to afford the acrylic acid **48**. The acrylic acid **48** is reduced in one or two steps to the propanol derivative **49**. The propanol derivative **49** is then converted to the primary amine or the substituted amine depending on whether

ammonia or a substituted amine is used to react with the propyl chloride derivative 50 formed from a halogenation reaction of the propanol derivative 49. The halogenation of the propanol derivative 49 is effected with thionyl chloride or other chlorinating agent. The chloride 50 is then displaced with an amine source to afford the desired amine component 51. The methoxy group of the amine 51 may be reduced to the hydroxy group using procedures described herein to afford the phenoxy compound 52. The phenoxy compound 52 may be coupled with a source of nicotinamide, benzamide, synthon thereof, or other source of the C-ring of compound of formula I to afford the compound 53, a compound of the invention.

### Method of Using the Invention

As noted above, the compounds of the present invention are useful in blocking the effect of agonists at mu, kappa, and/or delta opioid receptors. As such, the present invention also provides a method for blocking a mu, kappa, delta receptor or receptor combination (heterodimer) thereof in mammals comprising administering to a mammal requiring blocking of a mu, kappa, delta or combinations of mu, kappa, and/or delta receptors, a receptor blocking dose of a compound of formula I.

The term "receptor blocking dose", as used herein, means an amount of a compound of formula I necessary to block a mu, kappa, or delta receptor or receptor combination (heterodimer) thereof following administration to a mammal requiring blocking of a mu, kappa, or delta receptor or receptor combination (heterodimer) thereof.

The compounds of formula I or combinations thereof, are effective over a wide dosage range. For example, dosages per day will normally fall within the range of about 0.05 to about 250 mg/kg of body weight. In the treatment of adult humans, the range of about 0.05 to about 10 mg/kg, in single or divided doses, is preferred. However, it will be understood that the amount of the compound actually administered will be determined by a physician in light of the relevant circumstances, including the condition to be treated, the choice of compound to be administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the chosen route of administration, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. The compounds may be administered by a variety of routes

such as the oral, transdermal, subcutaneous, intranasal, intramuscular and intravenous routes.

A variety of physiologic functions have been shown to be subject to or influenced by mu, kappa, or delta receptors or receptor combination (heterodimers) in the brain. As such, the compounds of the present invention are believed to have the ability to treat a variety of disorders in mammals associated with these receptors or combinations thereof, such as eating disorders, opioid overdose, depression, smoking, alcoholism, sexual dysfunction, shock, stroke, spinal damage and head trauma. As such, the present invention also provides methods of treating the above disorders by blocking the effect of agonists at a mu, kappa, delta receptor or receptor combination (heterodimer) thereof. The compounds of the present invention have been found to display excellent activity in an opioid receptor binding assay which measures the ability of the compounds to block the mu, kappa, delta or receptor combination (heterodimer) thereof.

#### GTP- $\gamma$ -S Binding Assay

A scintillation proximity assay (SPA)- based GTP- $\gamma$ -S<sup>35</sup> assay format was developed based on previous opioid (Emmerson et al., J. Pharm Exp Ther 278,1121,1996; Hornig et al., Society for Neuroscience Abstracts, 434.6, 2000) and muscarinic (DeLapp et al., JFET 289, 946, 1999) assay formats. Membranes were resuspended in 20 mM HEPES, 100 mM NaCl, 5 mM MgCl<sub>2</sub>, 1 mM DTT, and 1 mM EDTA. Fifty mL of GTP- $\gamma$ -[35S], compound, membrane suspension (20 microgram/well), and wheat germ agglutinin coated SPA beads (1mg/well) were added to clear bottom 96 well assay plates. GDP (200 mM) was added to the membrane solution prior to addition to the assay plates. Plates were sealed and incubated for four hours at room temperature then placed in a refrigerator overnight to allow the beads to settle. Signal stability at 4 °C was determined to be > 60 hours. Plates were warmed to room temperature and counted in a Wallac Microbeta scintillation counter. For antagonist assays, specific agonists were added at the following concentrations: (MOR) DAMGO 1 micromolar, (DOR) DPDPE 30 nM, (KOR) U69593 300 nM. Kb's were determined by Cheng-Prusoff equation (see Cheng and Prusoff, Biochem. Pharmacol. 22, 3099, 1973). Results obtained for a sample of compounds of the invention in the GTP- $\gamma$ -S Binding Assay are shown in table 1 below.

Table 1

Compound of Example	IUPAC name	Mu Kb (nM)	Kappa Kb (nM)	Delta Kb (nM)
90	6-{1-[2-(4-Fluoro-phenyl)-ethylamino]-indan-5-yloxy}-nicotinamide	0.4	9.2	14.6
195	6-{5-[(2-Cyclohexyl-ethylamino)-methyl]-5,6,7,8-tetrahydro-naphthalen-1-yloxy}-nicotinamide	0.5	76.0	7.9
192	6-{5-[(3-Methyl-butylamino)-methyl]-5,6,7,8-tetrahydro-naphthalen-1-yloxy}-nicotinamide	1.1	11.8	9.4
202	6-{5-[(3,3-Dimethyl-butylamino)-methyl]-5,6,7,8-tetrahydro-naphthalen-1-yloxy}-nicotinamide	0.65	5.79	4.09
20	6-{1-[Methyl-(3-methyl-butyl)-amino]-indan-5-yloxy}-nicotinamide	0.73	2.5	13.48

### Formulation

While it is possible to administer a compound of the invention directly without any formulation, the compounds are preferably employed in the form of a pharmaceutical formulation comprising a pharmaceutically acceptable carrier, diluent or excipient and a compound of the invention. Such compositions will contain from about 0.1 percent by weight to about 90.0 percent by weight of a present compound. As such, the present

invention also provides pharmaceutical formulations comprising a compound of the invention and a pharmaceutically acceptable carrier, diluent or excipient thereof.

In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material that acts as a vehicle, excipient or medium for the active ingredient. Thus, the composition can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, emulsions, solutions, syrups, suspensions, aerosols (as a solid or in a liquid medium, and soft and hard gelatin capsules.

Examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, tragacanth, gelatin, syrup, methyl cellulose, methyl- and propylhydroxybenzoates, talc, magnesium stearate, water, and mineral oil. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

For oral administration, a compound of this invention ideally can be admixed with carriers and diluents and molded into tablets or enclosed in gelatin capsules.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 1 to about 500 mg, more usually about 5 to about 300 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier.

In order to more fully illustrate the operation of this invention, the following formulation examples are provided. The examples are illustrative only, and are not intended to limit the scope of the invention. The formulations may employ as active compounds any of the compounds of the present invention.

#### FORMULATION 1

Hard gelatin capsules are prepared using the following ingredients:

Compound	Amount per capsule (mg)	Concentration by weight (%)
Cyclohexyl-3-hydroxy-propyl)-3,4-dimethyl-piperidin-4-yl]-benzamide	250	55
Starch dried	200	43
Magnesium stearate	10	2

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

#### FORMULATION 2

Capsules each containing 20 mg of medicament are made as follows:

Compound	Amount per capsule (mg)	Concentration by weight (%)
Cyclohexyl-3-hydroxy-propyl)-3,4-dimethyl-piperidin-4-yl]-benzamide	20	10
Starch	89	44.5
Microcrystalline cellulose	89	44.5
Magnesium stearate	2	1

The active ingredient, cellulose, starch and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve and filled into a hard gelatin capsule.

#### FORMULATION 3

Capsules each containing 100 mg of active ingredient are made as follows:

Compound	Amount per capsule (mg)	Concentration by weight (%)
Cyclohexyl-3-hydroxy-propyl)-3,4-dimethyl-	100	30

piperidin-4-yl]-benzamide		
Polyoxyethylene Sorbitan monooleate	50mcg	0.02
Starch powder	250	69.98

The above ingredients are thoroughly mixed and placed in an empty gelatin capsule.

#### FORMULATION 4

Tablets each containing 10 mg of active ingredient are prepared as follows:

Compound	Amount per capsule (mg)	Concentration by weight (%)
Cyclohexyl-3-hydroxy-propyl)-3,4-dimethyl-piperidin-4-yl]-benzamide	10	10
Starch	45	45
Microcrystalline cellulose	35	35
Polyvinylpyrrolidone (as 10% solution in water)	4	4
Sodium carboxymethyl starch	4.5	4.5
Magnesium stearate	0.5	0.5
talc	1	1

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granule so produced is dried at 50-60 °C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granule which, after mixing, is compressed on a tablet machine to yield a tablet weighing 100 mg.

## FORMULATION 5

A tablet formula may be prepared using the ingredients below:

Compound	Amount per capsule (mg)	Percent by weight (%)
Cyclohexyl-3-hydroxy-propyl)-3,4-dimethyl-piperidin-4-yl]-benzamide	250	38
Cellulose microcrystalline	400	60
Silicon dioxide fumed	10	1.5
Stearic acid	5	0.5

The components are blended and compressed to form tablets each weighing 665 mg.

## FORMULATION 6

Suspensions each containing 5 mg of medicament per 5 ml dose are made as follows:

Compound	Amount per 5mL suspension (ml)
Cyclohexyl-3-hydroxy-propyl)-3,4-dimethyl-piperidin-4-yl]-benzamide	5
Sodium carboxymethyl cellulose	50
Syrup	1.25
Benzoic acid solution	0.10
Flavor	q.v.
Color	q.v.
Water	q.s. to 5mL

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethylcellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color is diluted with some of the water and added to the paste with stirring. Sufficient water is then added to produce the required volume.



## FORMULATION 7

An aerosol solution is prepared containing the following components:

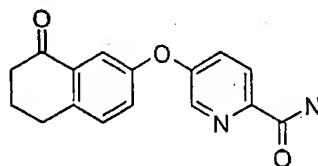
Compound	Concentration by weight (percent)
Cyclohexyl-3-hydroxy-propyl)-3,4-dimethyl-piperidin-4-yl]-benzamide hydrochloride	0.25
Ethanol	29.75
Propellant 22 (chlorodifluoromethane)	70.0

The active compound is mixed with ethanol and the mixture added to a portion of the Propellant 22, cooled to -30 °C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted further with the remaining amount of propellant. The valve units are then fitted to the container.

## Experimental Section

## Intermediate 1

5-(8-Oxo-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide.

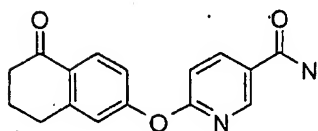


Combine 7-hydroxy-1-tetralone (J. Med. Chem. (1998), 41(7), 1068-1083), (3.37 g, 20.7 mmol), 6-chloronicotinamide (available from Aldrich Chemical Company, Milwaukee, USA) (2.95 g, 18.8 mmol, K<sub>2</sub>CO<sub>3</sub> (3.91 g, 28.3 mmol), DMA (dimethylacetamide) (45 ml) and toluene (25 ml) in a round bottom flask, equipped with Dean-Stark trap, condenser, and nitrogen inlet. Reflux the suspension for 2-3 hours before cooling to ambient temperature. Remove the solids via filtration, wash solids with

EtOAc, and concentrate the filtrate / wash on a rotary evaporator. Dissolve the remaining oil in EtOAc, wash with water (2x) and brine, dry ( $\text{MgSO}_4$ ) and concentrate. Triturate the resulting brown solid with boiling EtOAc, cool, and collect solid via filtration to give 4.76 g of the title compound as a yellow solid. Mass spectrum (ion spray):  $m/z = 283$  ( $M+1$ );  $^1\text{H}$ NMR ( $\text{DMSO}-d_6$ ): 8.56 (s, 1H), 8.25 (d, 1H), 8.02 (s, 1H), 7.52 (s, 1H), 7.48 (s, 1H), 7.42 (d, 1H), 7.35 (d, 1H), 7.12 (d, 1H), 2.95 (t, 2H), 2.60 (t, 2H), 2.05 (m, 2H).

### Intermediate 2

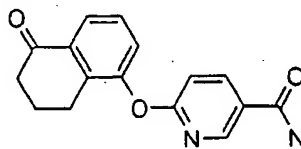
6-(5-Oxo-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide.



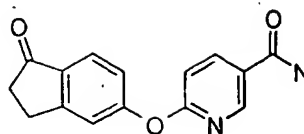
Using a method similar to Intermediate 1, using 6-hydroxy-1-tetralone (5.00 g, 30.8 mmol), 6-chloronicotinamide (4.38 g, 28.0 mmol) and  $\text{K}_2\text{CO}_3$  (5.81 g, 42.0 mmol) gives the title compound (5.7 g) as a yellow solid. Mass spectrum (ion spray):  $m/z = 283$  ( $M+1$ );  $^1\text{H}$ NMR ( $\text{DMSO}-d_6$ ): 8.63 (s, 1H), 8.29 (d, 1H), 8.06 (s, 1H), 7.90 (d, 1H), 7.51 (s, 1H), 7.16 (d, 1H), 7.12 (s, 1H), 7.09 (d, 1H), 2.92 (t, 2H), 2.58 (t, 2H), 2.03 (m, 2H).

### Intermediate 3

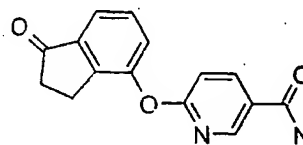
6-(5-Oxo-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide.



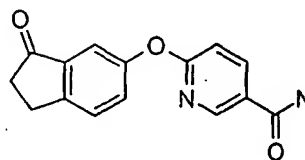
Using a method similar to Intermediate 1, using 5-hydroxy-1-tetralone (2.68 g, 16.5 mmol), 6-chloronicotinamide (2.34 g, 15.0 mmol) and  $\text{K}_2\text{CO}_3$  (3.11 g, 22.5 mmol) gives the title compound (2.34 g) as a yellow solid. Mass spectrum (ion spray):  $m/z = 283$  ( $M+1$ );  $^1\text{H}$ NMR ( $\text{DMSO}-d_6$ ): 8.55 (s, 1H), 8.27 (d, 1H), 8.02 (s, 1H), 7.80 (m, 1H), 7.48 (s, 1H), 7.43-7.37 (m, 1H), 7.14 (d, 1H), 2.66 (t, 2H), 2.58 (t, 2H), 1.96 (m, 2H).

**Intermediate 4****6-(1-Oxo-indan-5-yloxy)-nicotinamide.**

Using a method similar to Intermediate 1, using 5-hydroxy-1-indanone (2.44 g, 16.5 mmol), 6-chloronicotinamide (2.34 g, 15.0 mmol) and  $K_2CO_3$  (3.11 g, 22.5 mmol) gives the title compound (1.90 g) as a yellow solid. Mass spectrum (ion spray):  $m/z$  = 269 (M+1);  $^1H$ NMR (DMSO- $d_6$ ): 8.63 (s, 1H), 8.30 (d, 1H), 8.06 (s, 1H), 7.68 (d, 1H), 7.52 (s, 1H), 7.33 (s, 1H), 7.19 (d, 1H), 7.17 (d, 1H), 3.07 (t, 2H), 2.64 (t, 2H).

**Intermediate 5****6-(1-Oxo-indan-4-yloxy)-nicotinamide.**

Using a method similar to Intermediate 1, using 4-hydroxy-1-indanone (2.44 g, 16.5 mmol), 6-chloronicotinamide (2.34 g, 15.0 mmol) and  $K_2CO_3$  (3.11 g, 22.5 mmol) gives the title compound (1.22 g) as a yellow solid. Mass spectrum (ion spray):  $m/z$  = 269 (M+1);  $^1H$ NMR (DMSO- $d_6$ ): 8.57 (s, 1H), 8.29 (d, 1H), 8.03 (s, 1H), 7.55-7.46 (M, 4H), 7.19 (d, 1H), 2.81 (t, 2H), 2.61 (t, 2H).

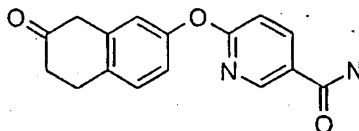
**Intermediate 6****6-(3-Oxo-indan-5-yloxy)-nicotinamide.**

Using a method similar to Intermediate 1, using 6-hydroxy-1-indanone (J. Med. Chem. (1998), 41(7), 1068-1083) (2.07 g, 13.9 mmol), 6-chloronicotinamide (2.08 g, 13.3 mmol) and  $K_2CO_3$  (2.75 g, 19.9 mmol) gives the title compound (1.36g) as a yellow solid. Mass spectrum (ion spray):  $m/z$  = 269 (M+1);  $^1H$ NMR (DMSO- $d_6$ ): 8.57 (s, 1H), 8.26

(d, 1H), 8.02 (s, 1H), 7.63 (d, 1H), 7.46 (m, 2H), 7.33 (s, 1H), 7.14 (d, 1H), 3.10 (t, 2H), 2.68 (t, 2H).

### Intermediate 7

6-(7-Oxo-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide.

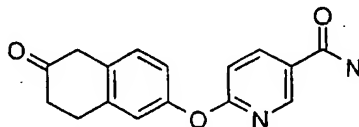


Combine 7-methoxy-2-tetralone (5.00 g, 28.3 mmol), thiophenol (3.39 g, 30.8 mmol),  $K_2CO_3$  (213 mg, 1.54 mmol), and NMP (15 ml) in a round bottom flask equipped with nitrogen inlet. Heat at  $180^\circ C$  for six hours and then stir at ambient temperature overnight. Treat reaction mixture with 1N aq. NaOH (20 ml) and water (20 ml) before extracting with  $Et_2O$ . Adjust the alkaline mixture to pH 4 with 1N aq. HCl and extract with  $Et_2O$  (3x). Dry ( $MgSO_4$ ) the ethereal layer and concentrate to a yellow solid. Purify the crude material on silica gel, eluting with 5% EtOAc/DCM, to obtain 7-hydroxy-2-tetralone (1.88 g) as a light red solid.  $^1H$ NMR ( $CDCl_3$ ): 7.09 (d, 1H), 6.69 (d, 1H), 6.62 (s, 1H), 4.86 (s, 1H), 3.53 (s, 2H), 2.99 (t, 2H), 2.54 (t, 2H).

Using a method similar to Example A, using 7-hydroxy-2-tetralone (1.88 g, 11.6 mmol), 6-chloronicotinamide (1.81 g, 11.6 mmol) and  $K_2CO_3$  (2.40 g, 17.4 mmol) gives the title compound (742 mg), after purification on silica gel (30% THF / DCM), as an amber foam. Mass spectrum (ion spray):  $m/z = 283$  (M+1);  $^1H$ NMR ( $DMSO-d_6$ ): 8.57 (s, 1H), 8.23 (d, 1H), 8.01 (s, 1H), 7.46 (s, 1H), 7.30 (d, 2H), 7.05 (d, 1H), 6.96 (m, 2H), 3.59 (s, 2H), 3.02 (t, 2H), 2.45 (t, 2H).

### Intermediate 8

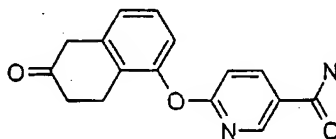
6-(6-Oxo-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide.



Using a method similar to Intermediate 1, using 6-hydroxy-2-tetralone (Journal of Organic Chemistry (1999), 64(26), 9719-9721.) (1.55 g, 9.55 mmol), 6-chloronicotinamide (1.49g, 9.55 mmol) and  $K_2CO_3$  (1.98 g, 14.3 mmol) gives the title compound (1.32 g), after purification on silica gel (50% THF/DCM), as an amber foam. Mass spectrum (ion spray):  $m/z = 283$  ( $M+1$ );  $^1H$ NMR ( $DMSO-d_6$ ): 8.59 (s, 1H), 8.23 (d, 1H), 8.01 (s, 1H), 7.47 (s, 1H), 7.19 (d, 2H), 7.07 (m, 2H), 6.97 (d, 1H), 3.59 (s, 2H), 3.01 (t, 2H), 2.43 (t, 2H).

#### Intermediate 9

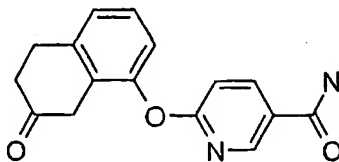
6-(6-Oxo-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide.



Using a method similar to Intermediate 1, using 5-hydroxy-2-tetralone (J. Med. Chem. (1978), 21(9), 913-22.) (1.98 g, 12.1 mmol), 6-chloronicotinamide (1.90g, 12.1 mmol) and  $K_2CO_3$  (2.52 g, 18.2 mmol) gives the title compound (1.80 g), after purification on silica gel (50% THF/DCM), as an amber foam. Mass spectrum (ion spray):  $m/z = 283$  ( $M+1$ );  $^1H$ NMR ( $DMSO-d_6$ ): 8.55 (s, 1H), 8.24 (d, 1H), 8.00 (s, 1H), 7.46 (s, 1H), 7.25 (d, 2H), 7.08 (m, 2H), 7.00 (d, 1H), 3.64 (s, 2H), 2.77 (t, 2H), 2.34 (t, 2H).

#### Intermediate 10

6-(7-Oxo-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide.

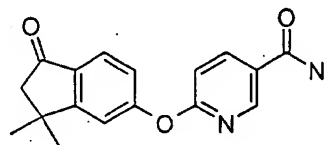


Using a method similar to Intermediate 1, using 8-hydroxy-2-tetralone (J. Med. Chem. (1978), 21(9), 913-22.) (1.55g, 9.55 mmol), 6-chloronicotinamide (1.49 g, 9.55 mmol) and  $K_2CO_3$  (1.98 g, 14.3 mmol) gives the title compound (652 mg), after

purification on silica gel (50% THF/DCM), as a yellow foam. Mass spectrum (ion spray):  $m/z = 283$  ( $M+1$ );  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ): 8.52 (s, 1H), 8.18 (d, 1H), 7.30 (t, 1H), 7.17 (d, 1H), 7.02 (m, 2H), 5.92 (broad, 2H), 3.42 (s, 2H), 3.15 (t, 2H), 2.61 (t, 2H).

### Intermediate 11

#### 6-(3,3-Dimethyl-1-oxo-indan-5-yloxy)-nicotinamide.



Add drop-wise a solution of  $\text{BBr}_3$  (8.14g, 32.5 mmol) dissolved in DCM (10ml) to a solution of 5-Methoxy-3,3-dimethyl-1-indanone (US6313107) (2.47g, 13.0 mmol) dissolved in DCM (20ml) and cooled to  $-78^\circ\text{C}$  under nitrogen. After stirring at  $-78^\circ\text{C}$  for one hour, remove the cold bath and stir at ambient temperature overnight. Cool the reaction mixture to  $-78^\circ\text{C}$  and quench with saturated aqueous  $\text{NaHCO}_3$ . Dilute mixture with water and extract with EtOAc (2x). Wash extracts with water and brine, dry ( $\text{MgSO}_4$ ) and concentrate on rotary evaporator to a dark amber solid. Triturate the solid with boiling  $\text{Et}_2\text{O}$ , cool, and collect 5-hydroxy-3,3-dimethyl-1-indanone (1.54 g) as a tan solid.

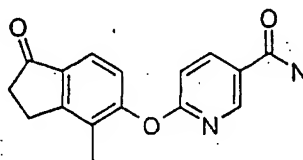
Add NaH (60%/oil, 196 mg, 4.91 mmol) to a mixture of 5-hydroxy-3,3-dimethyl-1-indanone (787 mg, 4.46 mmol) and DMSO (10ml) stirring at ambient temperature under nitrogen. After ten minutes, add 6-chloronicotinonitrile (619 mg, 4.46 mmol) dissolved in DMSO (10 ml) and stir the resulting mixture at  $60^\circ\text{C}$  overnight. Quench the reaction with saturated aqueous  $\text{NH}_4\text{Cl}$  and extract with EtOAc (2x). Wash extract with water and brine, dry ( $\text{MgSO}_4$ ) and concentrate on rotary evaporator to a brown, oily solid. Purify on silica gel (10% EtOAc/DCM) to give 877 mg of 6-(3,3-Dimethyl-1-oxo-indan-5-yloxy)-nicotinonitrile as a yellow solid.

Add 30% aqueous  $\text{H}_2\text{O}_2$  (3.15 ml) to a suspension of 6-(3,3-Dimethyl-1-oxo-indan-5-yloxy)-nicotinonitrile (877 mg, 3.15 mmol),  $\text{K}_2\text{CO}_3$  (218 mg, 1.57 mmol) and DMSO (10 ml) stirring under nitrogen at ambient temperature. After four hours, dilute the reaction mixture with water (100 ml) and extract with EtOAc (2x). Wash the extract with water and brine, dry ( $\text{MgSO}_4$ ) and concentrate on rotary evaporator to yield 876 mg

of the title compound as an off-white solid. Mass spectrum (ion spray):  $m/z = 297$  ( $M+1$ );  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ): 8.62 (s, 1H), 8.24 (d, 1H), 7.75 (d, 1H), 7.24 (s, 1H), 7.14 (d, 1H), 7.07 (d, 1H), 5.91 (broad, 2H), 2.63 (s, 2H), 1.43 (s, 6H).

### Intermediate 12

#### 6-(4-Methyl-1-oxo-indan-5-yloxy)-nicotinamide.



Add drop-wise a solution of  $\text{BBr}_3$  (14.8 g, 59.1 mmol) dissolved in DCM (50 ml) to a solution of 5-Methoxy-4-methyl-1-indanone (Tetrahedron (1970), 26(11), 2599-608) (4.17 g, 23.6 mmol) dissolved in DCM (50 ml) and cooled to  $-78^\circ\text{C}$  under nitrogen. After stirring at  $-78^\circ\text{C}$  for one hour, remove the cold bath and stir at ambient temperature overnight. Cool the reaction mixture to  $-78^\circ\text{C}$  and quench with saturated aqueous  $\text{NaHCO}_3$ . Dilute mixture with water and extract with EtOAc (2x). Wash extracts with water and brine, dry ( $\text{MgSO}_4$ ) and concentrate on rotary evaporator to give 5-hydroxy-4-methyl-1-indanone (2.60 g) as an amber solid.

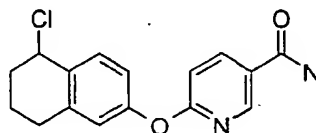
Add  $\text{K}_2\text{CO}_3$  (1.24 g, 9.00 mmol) to a mixture of 5-hydroxy-4-methyl-1-indanone (973 mg, 6.00 mmol), 6-chloronicotinonitrile (831 mg, 6.00 mmol) and DMSO (15ml) stirring at ambient temperature under nitrogen. Heat the mixture at  $55^\circ\text{C}$  for three days. Quench the reaction with saturated aqueous  $\text{NH}_4\text{Cl}$  and extract with EtOAc (2x). Wash extract with water and brine, dry ( $\text{MgSO}_4$ ) and concentrate on rotary evaporator to a brown foam. Purify on silica gel (10% EtOAc/DCM) to give 1.22 g of 6-(4-Methyl-1-oxo-indan-5-yloxy)-nicotinonitrile as a yellow solid.

Add 30% aqueous  $\text{H}_2\text{O}_2$  (3.6 ml) to a suspension of 6-(4-Methyl-1-oxo-indan-5-yloxy)-nicotinonitrile (1.22 mg, 4.61 mmol),  $\text{K}_2\text{CO}_3$  (319 mg, 2.31 mmol) and DMSO (20 ml) stirring under nitrogen at ambient temperature. After 2.5 hours, dilute the reaction mixture with water (100ml) and extract with EtOAc (2x). Wash the extract with water and brine, dry ( $\text{MgSO}_4$ ) and concentrate on rotary evaporator to yield 1.07 g of the title compound as a yellow solid. Mass spectrum (ion spray):  $m/z = 283$  ( $M+1$ );  $^1\text{H NMR}$

(DMSO- $d_6$ ): 8.55 (s, 1H), 8.27 (d, 1H), 8.01 (s, 1H), 7.51 (d, 1H), 7.47 (s, 1H), 7.17 (d, 1H), 7.12 (d, 1H), 3.03 (t, 2H), 2.66 (t, 2H), 2.07 (s, 3H).

### Intermediate 13

6-(5-Chloro-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide.

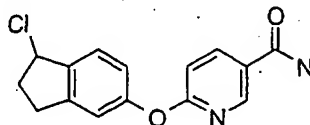


Add  $\text{NaBH}_4$  (79.4 mg, 2.10 mmol) to a suspension of 6-(5-Oxo-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide (Intermediate 2, 395 mg, 1.40 mmol) in MeOH (10 ml), stirring at ambient temperature. After 24 hours, concentrate the reaction mixture and redissolve in EtOAc. Wash with 5% aqueous KOH, water, and brine before drying ( $\text{MgSO}_4$ ) and concentrating to a solid. Purify material on silica gel (50% THF/DCM) to give 6-(5-Hydroxy-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide (288 mg) as a white solid. Mass spectrum (ion spray):  $m/z = 285$  ( $M+1$ );  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ): 8.58 (s, 1H), 8.16 (d, 1H), 7.50 (d, 1H), 6.97 (m, 2H), 6.88 (s, 1H), 5.95 (broad, 2H), 4.80 (t, 1H), 2.82-2.74 (m, 2H), 2.03-1.77 (m, 4H), 1.68 (s, 1H).

Charge flask with 6-(5-Hydroxy-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide (288 mg, 1.01 mmol) and  $\text{SOCl}_2$  (5 ml) and heat at  $50^\circ\text{C}$  under nitrogen atmosphere with stirring. After 3.5 hours, concentrate on rotary evaporator to give the title compound as a yellow oil. Due to instability, use this material without purification.

### Intermediate 14

6-(1-Chloro-indan-5-yloxy)-nicotinamide

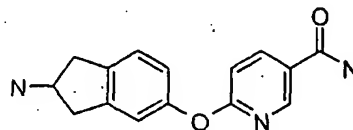


Using a method similar to intermediate 13, using 6-(1-Oxo-indan-5-yloxy)-nicotinamide (Intermediate 4, 500 mg, 1.86 mmol) and  $\text{NaBH}_4$  (105 mg, 2.79 mmol) gives 6-(1-Hydroxy-indan-5-yloxy)-nicotinamide (346 mg) as a white solid. Mass spectrum (ion spray):  $m/z = 271$  ( $M+1$ );  $^1\text{H}$ NMR (DMSO- $d_6$ ): 8.58 (s, 1H), 8.22 (d, 1H),



8.00 (s, 1H), 7.45 (s, 1H), 7.34 (d, 1H), 7.03 (d, 1H), 6.97 (s, 1H), 6.93 (d, 1H), 5.03 (t, 1H), 2.93-2.86 (m, 1H), 2.73-2.66 (m, 1H), 2.38-2.30 (m, 1H), 1.84-1.72 (m, 1H), 1.33 (s, 1H). Convert 6-(1-Hydroxy-indan-5-yloxy)-nicotinamide to the title compound using a method similar to intermediate 13. Due to instability, use this material without purification.

### Intermediate 15



#### 6-(2-Amino-indan-5-yloxy)-nicotinamide.

Reflux a mixture of 5-methoxy-2-aminoindane prepared according to Hajduk, Philip J., et al.; *J. Med. Chem.* 1999, 42, 3852 - 3859. (2.76 g, 16.9 mmol) and 48% aqueous HBr for three hours before cooling and concentrating on rotary evaporator. Treat the crude 5-hydroxy-2-aminoindane with THF (50 ml), 1M aqueous  $K_2CO_3$  (42 ml), and  $Boc_2O$  (4.05 g, 18.6 mmol) and stir at ambient temperature overnight. Pour mixture into saturated aqueous  $NH_4Cl$  and extract with EtOAc (2x). Wash combined extracts with brine, dry ( $MgSO_4$ ) and concentrate to a brown foam. Purify on silica gel (10% EtOAc/ DCM) to give N-Boc-5-hydroxy-2-aminoindane (2.50 g) as a tan solid.

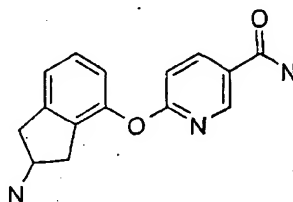
Combine N-Boc-5-hydroxy-2-aminoindane (2.50 g, 10.0 mmol), 6-chloronicotinamide (1.49 g, 9.55 mmol,  $K_2CO_3$  (1.90 g, 14.3 mmol), DMA (25 ml) and toluene (20 ml) in a round bottom flask, equipped with Dean-Stark trap, condenser, and nitrogen inlet. Reflux the suspension for two hours before cooling to ambient temperature. Remove the solids via filtration, wash solids with EtOAc, and concentrate the filtrate / wash on a rotary evaporator. Dissolve the remaining oil in EtOAc, wash with water (2x) and brine, dry ( $MgSO_4$ ) and concentrate. Purify the material on silica gel (20% THF/DCM) to give [5-(5-carbamoyl-pyridin-2-yloxy)-indan-2-yl]-carbamic acid tert-butyl ester (870 mg) as a light yellow solid.

Add TFA (5.37 g, 47.1 mmol) to a suspension of [5-(5-carbamoyl-pyridin-2-yloxy)-indan-2-yl]-carbamic acid tert-butyl ester (870 mg, 2.35 mmol) in DCM (30 ml) and stir at ambient temperature overnight. Concentrate mixture on rotary evaporator and purify on cation exchange column (5 g, Varian) to give the title compound (479 mg) as a

white solid. Mass spectrum (ion spray):  $m/z = 270$  ( $M+1$ );  $^1\text{H}$ NMR ( $\text{MeOH-}d_4$ ): 8.61 (s, 1H), 8.22 (d, 1H), 7.24 (d, 1H), 6.98 (s, 1H), 6.94 (d, 1H), 6.90 (d, 1H), 3.80 (m, 1H), 3.18 (m, 2H), 2.72 (m, 2H).

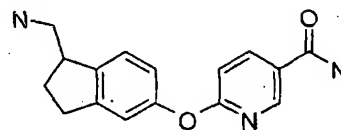
### Intermediate 16

6-(2-Amino-indan-4-yloxy)-nicotinamide.



Using a method similar to intermediate 15, using 4-methoxy-2-aminoindane (J. Med. Chem. (1985), 28(4), 515-18, 6.64 g, 40.6 mmol) gives the title compound (2.26 g) as a white solid. Mass spectrum (ion spray):  $m/z = 270$  ( $M+1$ );  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ): 8.54 (s, 1H), 8.14 (d, 1H), 7.23 (t, 1H), 7.12 (d, 1H), 6.93 (m, 2H), 6.19 (br s, 2H), 3.81 (m, 1H), 3.22 (dd, 1H), 2.94 (dd, 1H), 2.71 (dd, 1H), 2.44 (dd, 1H).

### Intermediate 17



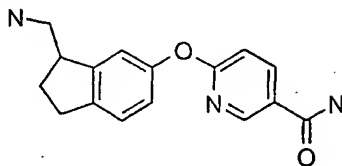
6-(1-Aminomethyl-indan-5-yloxy)-nicotinamide.

Dissolve sodium metal (1.51 g, 66.0 mmol) in abs. EtOH (50 ml) and DME (100 ml) and add the resulting solution drop-wise to a mixture of 5-methoxy-1-indanone (3.57 g, 22.0 mmol), tosylmethyl isocyanide (6.45 g, 33.0 mmol) and DME (150 ml) cooled to  $-5^\circ\text{C}$  under nitrogen. After addition is complete (ca. one hour), allow mixture to slowly obtain ambient temperature and stir overnight. After cooling to  $0^\circ\text{C}$ , carefully quench with water and extract with EtOAc (2x). Wash the combined extracts with water and brine, dry ( $\text{MgSO}_4$ ) and concentrate. Purify on silica gel (toluene) to give 5-methoxy-indan-1-carbonitrile (2.55 g) as a yellow oil.  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ): 7.31 (d, 1H), 6.80 (m, 2H), 4.05 (t, 1H), 3.80 (s, 3H), 3.07 (m, 1H), 2.93 (m, 1H), 2.56 (m, 1H), 2.39 (m, 1H).

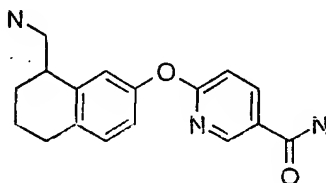
Subject a mixture of 5-methoxy-indan-1-carbonitrile (1.49 g, 8.60 mmol), Raney nickel (500 mg), anhydrous ammonia (10 ml), and abs. EtOH (50 ml) to 900 lbs of hydrogen gas and heat at 80°C for five hours. After cooling and purging with nitrogen, remove the catalyst via filtration and concentrate the filtrate on a rotary evaporator. Suspend this material in DCM (30 ml) and cool to -78°C before adding a solution of BBr<sub>3</sub> / DCM (8 ml) drop-wise. After the addition is complete, allow the mixture to warm to ambient temperature and stir for 2.5 hours. Cool again to -78°C and carefully quench with MeOH before concentrating. Treat this material with THF (35 ml), 1M aqueous K<sub>2</sub>CO<sub>3</sub> (21.5 ml), and Boc<sub>2</sub>O (2.25 g, 10.3 mmol) and stir vigorously at ambient temperature overnight. Pour the reaction mixture into saturated aqueous NH<sub>4</sub>Cl and extract with EtOAc (2x). Wash combined extracts with brine, dry (MgSO<sub>4</sub>) and concentrate to a yellow foam. Purify on silica gel (10% EtOAc/DCM) to obtain N-Boc-1-aminomethyl-indan-5-ol (945 mg) as a yellow foam. <sup>1</sup>HNMR (CDCl<sub>3</sub>): 6.98 (d, 1H), 6.85 (s, 1H), 6.73 (s, 1H), 6.65 (d, 1H), 4.69 (br s, 1H), 3.45 (m, 1H), 3.22 (m, 2H), 2.88-2.72 (m, 2H), 2.20 (m, 1H), 1.78 (m, 1H), 1.45 (s, 9H).

Heat a mixture of N-Boc-1-aminomethyl-indan-5-ol (1.13 g, 4.29 mmol), 6-chloronicotinamide (671 mg, 4.29 mmol, K<sub>2</sub>CO<sub>3</sub> (889 mg, 6.43 mmol), and DMSO (10 ml) at 100°C for 19 hours. Pour the reaction mixture into saturated aqueous NH<sub>4</sub>Cl and extract with EtOAc. Wash extract with brine, dry (MgSO<sub>4</sub>) and concentrate to a brown foam. Purify on silica gel (30% EtOAc/DCM) to obtain [5-(5-carbamoyl-pyridin-2-yloxy)-indan-1-ylmethyl]-carbamic acid tert-butyl ester (847 mg) as a light yellow solid. <sup>1</sup>HNMR (CDCl<sub>3</sub>): 8.61 (s, 1H), 8.17 (d, 1H), 7.24 (d, 1H), 7.00 (s, 1H), 6.95 (m, 3H), 6.03 (br s, 2H), 4.65 (br s, 1H), 3.48 (m, 1H), 3.31 (m, 2H), 2.98-2.83 (m, 2H), 2.30 (m, 1H), 1.90 (m, 1H), 1.45 (s, 9H).

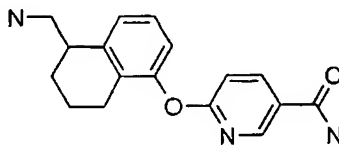
Add TFA (6.54 g, 57.4 mmol) to a suspension of [5-(5-carbamoyl-pyridin-2-yloxy)-indan-1-ylmethyl]-carbamic acid tert-butyl ester (1.05 g, 2.87 mmol) in DCM (20 ml) and stir at ambient temperature for four hours. Concentrate mixture on rotary evaporator and purify on cation exchange column (10 g, Varian) to give the title compound (519 mg) as a white solid. Mass spectrum (ion spray): m/z = 284 (M+1); <sup>1</sup>HNMR (DMSO-d<sub>6</sub>): 8.58 (s, 1H), 8.21 (d, 1H), 8.00 (br s, 1H), 7.44 (br s, 1H), 7.27 (d, 1H), 7.01 (d, 1H), 6.96 (s, 1H), 6.87 (d, 1H), 3.05 (m, 1H), 2.84 (m, 2H), 2.77 (m, 1H), 2.62 (m, 1H), 2.18 (m, 1H), 1.82 (m, 1H), 1.71 (br s, 2H).

**Intermediate 18****6-(3-Aminomethyl-indan-5-yloxy)-nicotinamide.**

Using a method similar to intermediate 17, using 6-methoxy-1-indanone gave the title compound as a light yellow solid. Mass spectrum (ion spray):  $m/z = 284$  ( $M+1$ );  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ): 8.59 (s, 1H), 8.15 (d, 1H), 7.25 (d, 1H), 7.00 (s, 1H), 6.94 (d, 2H), 6.12 (br s, 2H), 3.23 (m, 1H), 2.99-2.84 (m, 4H), 2.33 (m, 1H), 1.89 (m, 1H), 1.40 (br s, 2H).

**Intermediate 19****6-(8-Aminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide.**

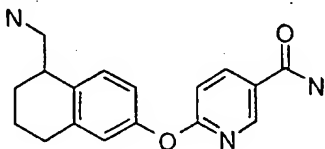
Using a method similar to intermediate 17, using 6-methoxy-1-tetralone gave the title compound as a light amber solid. Mass spectrum (ion spray):  $m/z = 298$  ( $M+1$ );  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ): 8.58 (s, 1H), 8.15 (d, 1H), 7.13 (d, 1H), 6.99 (s, 1H), 6.95 (d, 1H), 6.90 (d, 1H), 6.01 (br s, 2H), 2.93 (d, 2H), 2.81 (m, 1H), 2.77 (m, 2H), 1.91-1.70 (m, 8H).

**Intermediate 20****6-(5-Aminomethyl-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide.**

Using a method similar to intermediate 17, using 5-methoxy-1-tetralone gave the title compound as a light tan solid. Mass spectrum (ion spray):  $m/z = 298$  ( $M+1$ );  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ): 8.57 (s, 1H), 8.16 (d, 1H), 7.23-7.12 (m, 2H), 6.94-6.90 (m, 2H), 5.83 (br s, 2H), 3.03-2.82 (m, 3H), 2.62-2.47 (m, 2H), 1.88-1.66 (m, 4H), 1.34 (br s, 2H).

#### Intermediate 21

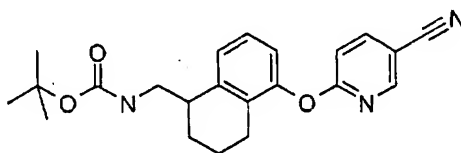
6-(5-Aminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide.



Using a method similar to intermediate 17, using 6-methoxy-1-tetralone gave the title compound as a white foam. Mass spectrum (ion spray):  $m/z = 298$  ( $M+1$ );  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ): 8.59 (s, 1H), 8.16 (d, 1H), 7.25 (d, 1H), 6.94 (d, 1H), 6.90 (d, 1H), 6.86 (s, 1H), 5.92 (br s, 2H), 3.00-2.90 (m, 2H), 2.85-2.79 (m, 1H), 2.78-2.73 (m, 2H), 1.89-1.69 (m, 4H), 1.34 (br s, 2H).

#### Intermediate 22

[5-(5-Cyano-pyridin-2-yloxy)-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-carbamic acid tert-butyl ester.

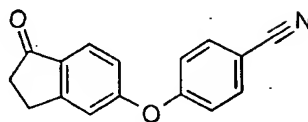


acid tert-butyl ester.

Combine N-Boc-1-aminomethyl-indan-5-ol (described in prep for Intermediate 17) (5.80 g, 20.9 mmol), 6-chloronicotinonitrile (2.89 g, 20.9 mmol),  $\text{K}_2\text{CO}_3$  (4.33 g, 31.3 mmol) and DMA (50 ml) and heat at 100 C for 4.5 hours. After cooling, pour the reaction mixture into saturated, aqueous  $\text{NH}_4\text{Cl}$  and extract with EtOAc (2x). Wash extract with brine, dry ( $\text{MgSO}_4$ ) and concentrate to a brown foam. Purify on silica gel (30% EtOAc/Hexane) to obtain the title compound (7.88 g) as a light yellow foam. Mass spectrum (ion spray):  $m/z = 380$  ( $M+1$ );  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ): 8.45 (s, 1H), 7.90 (d, 1H), 7.25-7.18 (m, 2H), 6.99 (d, 1H), 6.91 (d, 1H), 4.69 (m, 1H), 3.51-3.25 (m, 2H), 3.03 (m, 1H), 2.62-2.39 (m, 1H), 1.83-1.68 (m, 4H), 1.46 (s, 9H).

## Intermediate 23

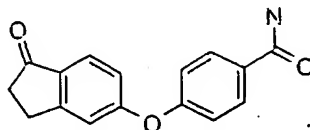
## 4-(1-Oxo-indan-5-yloxy)-benzonitrile.



Combine 5-Hydroxyindanone (2.0g, 13.50 mmol), 4-Fluorobenzonitrile (1.55g, 12.80 mmol),  $K_2CO_3$  (2.65 g, 19.20 mmol) and toluene/DMA (20ml/40ml), reflux under Nitrogen using a Dean-Stark Trap. After 4.0 hours, cool the reaction to room temperature and add Ethyl Acetate. Wash several times with 10% LiCl and Brine solution, then dry the organic layer over  $Na_2SO_4$  follow by concentration. Flash chromatograph using 4/1 then 1/1 hexanes/ethyl acetate eluant to afford 1.64 g, 6.57 mmol (49% yield) of the title compound:  $^1H$  NMR (500 MHz,  $CDCl_3$ ); 2.7-2.8 (2H, m), 3.1-3.2 (2H, m), 7.0-7.1 (2H, m), 7.1-7.2 (2H, m), 7.6-7.7 (2H, m), 7.7-7.8 (1H, m); MS  $m/z$  250 (M+1).

## Intermediate 24

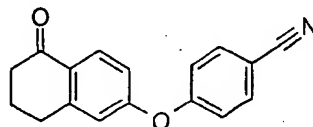
## 4-(1-Oxo-indan-5-yloxy)-benzamide.



Combine 4-(1-Oxo-indan-5-yloxy)-benzonitrile (1.64g, 6.58 mmol), *tert*-butyl alcohol (50 ml), and grounded KOH (1.85g, 32.89 mmol) at room temperature under nitrogen atmosphere. Stir the reaction for 24 hours then concentrate under reduced pressure. Add Ethyl acetate to the reaction mixture and wash with brine. Dry the organic layer over  $Na_2SO_4$ . A yellow-orange solid precipitates out to afford 101.0 mg, 0.38 mmol (5.7% yield) of the title compound: No Characterization—Characterized by sequential reaction.

## Intermediate 25

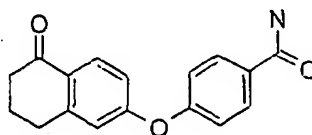
4-(5-Oxo-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-benzonitrile.



Combine 6-Hydroxytetralone (4.42g, 27.24 mmol), 4-Fluorobenzonitrile (3.0g, 24.76 mmol),  $K_2CO_3$  (5.1g, 37.14 mmol) and toluene/DMA (30ml/90ml), then reflux under nitrogen using a Dean Stark Trap. After 4 hours, cool the reaction to room temperature and add to a separatory funnel. Add Ethyl acetate and wash the organic layer several times with water, then a brine solution, and dry the organic layer over  $Na_2SO_4$ . Flash chromatograph using 4/1 hexanes/ethyl acetate eluant to afford 5.34 g, 20.3 mmol (82% yield) of the title compound:  $^1H$  NMR (500 MHz,  $CDCl_3$ ); 2.1-2.2 (2H, m), 2.6-2.7 (2H, m), 2.9-3.0 (2H, m), 6.85 (1H, s), 6.9-7.0 (1H, m), 7.05-7.15 (2H, m), 7.6-7.7 (2H, m), 8.05-8.10 (1H, m); MS  $m/z$  264 ( $M+1$ ).

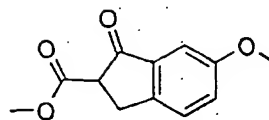
## Intermediate 26

4-(5-Oxo-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-benzamide.

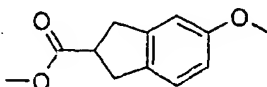


Combine 4-(5-Oxo-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-benzonitrile (5.34, 20.3 mmol), *t*-butyl alcohol (100ml), and KOH (5.7g, 101.5 mmol). After the reaction stirs for 72 hours at room temperature, concentrate under reduced pressure and then add ethyl acetate. Wash the organic phase with water, a brine solution, and then dry the organic layer over  $Na_2SO_4$ . Flash chromatograph using 2/1  $CH_2Cl_2$ /ethyl acetate eluent to afford 5.20 g, 18.5 mmol (91% yield) of the title compound:  $^1H$  NMR (500 MHz,  $CDCl_3$ ); 2.1-2.2 (2H, m), 2.6-2.7 (2H, m), 2.9-3.0 (2H, m), 5.6-6.2 9 (2H, br m), 6.85 (1H, s), 6.9-7.0 (1H, m), 7.05-7.15 (2H, m), 7.8-7.9 (2H, m), 8.05-8.10 (1H, m); MS  $m/z$  284 ( $M+3$ ).

## Intermediate 27

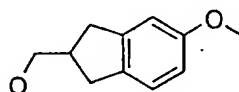
**6-Methoxy-1-oxo-indan-2-carboxylic acid methyl ester.**

Combine NaH (5.4g, 122.1 mmol), THF anhydrous (150 mL), and dimethylcarbonate (6.6mL, 81.3 mmol). While refluxing the reaction under a nitrogen atmosphere, add dropwise 5-Methoxyindanone (3.46g, 21.33 mmol) over one hour. After the reaction mixture refluxes for 12 hours, quench using Acetic acid and then add Ethyl acetate to the reaction mixture in a separatory funnel. Wash the organic layer several times with water and dry the organic layer over Na<sub>2</sub>SO<sub>4</sub> followed by concentration under reduced pressure. Flash.Chromatograph using 1:1 Hexanes:Ethyl acetate to afford 3.14g, 14.3 mmol (67% yield) of the title compound: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>); 3.3-3.4 (1H, dd), 3.5-3.6 (1H, dd), 3.7-3.8 (1H, m), 3.8 (3H, s), 3.9 (3H, s), 6.8-7.0 (2H, m), 7.7-7.8 (1H, m); TLC 2:1 Hexanes: Ethyl acetate R<sub>f</sub>=0.4.

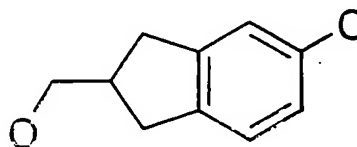
**Intermediate 28****5-Methoxy-indan-2-carboxylic acid methyl ester.**

Combine in a Parr shaker 6-Methoxy-1-oxo-indan-2-carboxylic acid methyl ester (3.14g, 14.25 mmol), added acetic acid (150 mL), perchloric acid (0.8mL) and 5% Pd-C (0.14 mmol). After the reaction has been on the parr shaker under 40 atm of H<sub>2</sub> pressure at room temperature for 12 hours, filter the reaction mixture through a pad of Celite using ethyl acetate eluent. Then add the filtrate to a separatory funnel and wash with water then brine, and dry the organic layer over Na<sub>2</sub>SO<sub>4</sub>. After concentrating under reduced pressure, flash Chromatograph using 8:1 Hexanes:Ethyl acetate to afford 1.9g, 9.21mmol (65% yield) of the title compound as a clear oil: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>); 3.2-3.4 (5H, m), 3.7 (3H, s), 3.8 (3H, s), 6.7-6.8 (2H, m), 7.1-7.2 (1H, m); TLC 1:1 Hexanes: Ethyl acetate R<sub>f</sub>=0.6.



**Intermediate 29****(5-Methoxy-indan-2-yl)-methanol.**

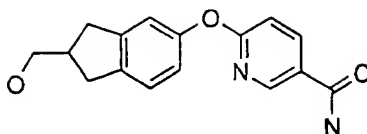
Combine 5-Methoxy-indan-2-carboxylic acid methyl ester (Intermediate 28, 1.90g, 9.21 mmol),  $\text{LiAlH}_4$  (0.70g, 18.43mmol), and THF anhydrous (60 ml). After the reaction stirs under a nitrogen atmosphere at room temperature for 2 hours, quench the reaction mixture with 5mL of deionized water. Filter the mixture through a pad of Celite using EtOAc eluent, and wash the organic layer with brine, and dry over  $\text{Na}_2\text{SO}_4$ . After concentrating under reduced pressure, the flash chromatograph the mixture to afford 1.43g, 8.0 mmol (87% yield) of the title compound as a clear oil:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 1.4-1.6 (1H, br s), 2.6-2.8 (3H, m), 2.9-3.2 (2H, m), 3.6-3.7 (2H, m), 3.8 (3H, s), 6.7-6.8 (2H, m), 7.1-7.2 (1H, m); TLC 1:1 Hexanes: Ethyl acetate  $R_f$ =0.4.

**Intermediate 30****2-Hydroxymethyl-indan-5-ol.**

Combine (5-Methoxy-indan-2-yl)-methanol (117.0 mg, 0.65 mmol), and 48%  $\text{HBr(aq)}$ . After the reaction refluxes for 30 minutes, cool to room temperature and extract the product with ethyl acetate. Wash with brine and dry over  $\text{Na}_2\text{SO}_4$ . After concentrating the organic layer under reduced pressure, flash chromatograph using 2/1 Hexanes/Ethyl acetate eluent to afford 67.3 mg, 0.41 mmol (63% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 2.6-2.8 (3H, m), 2.9-3.1 (2H, m), 3.6-3.8 (2H, m), 6.6-6.8 (2H, m), 7.0-7.1 (1H, m); TLC 1:1 Hexanes: Ethyl acetate  $R_f$ =0.3.

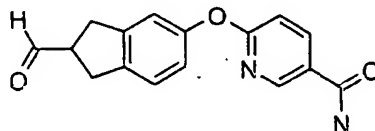
**Intermediate 31****6-(2-Hydroxymethyl-indan-5-yloxy)nicotinamide.**

60



Combine in a round bottom flask equipped with a stir, Dean Stark Trap filled with toluene, and reflux condenser 2-Hydroxymethyl-indan-5-ol (630.2 mg, 3.84 mmol),  $K_2CO_3$  (690.0 mg, 5.0 mmol), 6-Chloronicotinamide (600.0 mg, 3.84 mmol) and a solution of DMA:Toluene (15:5 mL). After the reaction refluxes under nitrogen atmosphere for 5 hours, concentrate under reduced pressure and then add ethyl acetate. Wash the organic layer several times with water, then brine, and dry over  $Na_2SO_4$ . After concentrating the reaction mixture under reduced pressure, flash chromatograph using 20% THF, 7% 1N  $NH_3$ -MeOH, 73% DCM eluent to afford 481.1mg, 1.69 mmol (44% yield) of the title compound:  $^1H$  NMR (500 MHz,  $CDCl_3$ ); 1.8-2.2 (4H, m), 2.6-2.8 (3H, m), 3.6-3.8 (2H, br d), 3.9-4.0 (1H, m), 6.1-6.6 (2H, br d), 6.8-7.0 (3H, m), 7.2-7.3 (1H, m), 8.1-8.2 (1H, m), 8.6 (1H, s); MS  $m/z$  285 (M+1).

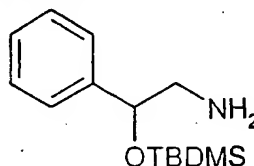
#### Intermediate 32



#### 6-(2-Formyl-indan-5-yl)oxy)-nicotinamide.

Combine DCM (3mL) and oxalyl chloride (41  $\mu$ L) under nitrogen atmosphere at  $-78^\circ C$ , and then add DMSO (49  $\mu$ L) in DCM (2mL). After the solution stirs for 15 minutes, add 6-(2-Hydroxymethyl-indan-5-yl)oxy)nicotinamide (33.1 mg, 0.116 mmol) in DCM (2 mL). After 15 minutes, add  $Et_3N$  (97  $\mu$ L, 0.70 mmol). After the reaction gradually warms to room temperature over the next 5 hours, then quench with water. Add the mixture to a separatory funnel and extract the product with DCM. Wash the organic phase with brine and then dry over  $Na_2SO_4$ . After concentrating under reduced pressure, flash chromatograph using 10% THF/ $CH_2Cl_2$  eluent affords 27.4 mg, 0.10 mmol (84% yield) of the title compound:  $^1H$  NMR (500 MHz,  $CDCl_3$ ); 3.1-3.2 (2H, m), 3.2-3.4 (3H, m), 6.8-7.0 (4H, m), 7.1-7.3 (1H, m), 8.8-8.9 (1H, m), 8.4 (1H, s), 9.7 (1H, s); TLC 1:6 THF:  $CH_2Cl_2$   $R_f$ =0.7.

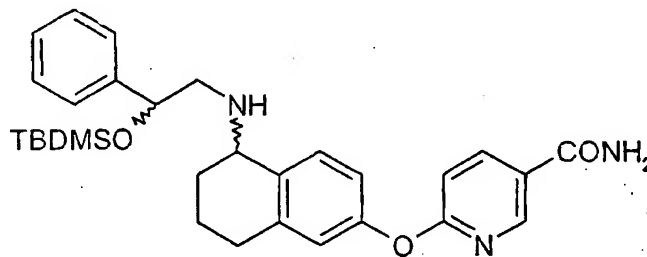
**Intermediate 33**  
**2-Tert-butyldimethylsilyloxyphenethyl amine.**



To a solution of TBDMSCl (2.1 equiv) and DBU (2.1 equiv) in  $\text{CH}_2\text{Cl}_2$  (0.5 M), add the alcohol (1 equiv). Stir the resulting reaction mixture under  $\text{N}_2$  at room temperature 3 hours. Wash the reaction mixture with water, 0.5% HCl and saturated aqueous solution of  $\text{NaHCO}_3$ , separate the organic layer, and dry over anhydrous  $\text{NaSO}_4$ . Evaporation of the solvent yields a residue which is purified by flash chromatography using  $\text{EtOAc}/\text{CH}_2\text{Cl}_2/2\text{M NH}_3$  in methanol, 0.6/0.35/0.05 to afford the title compound. 92% Yield.

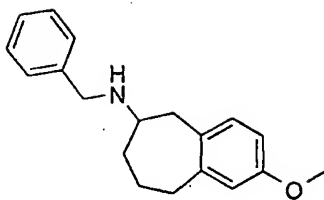
$^1\text{H}$  NMR ( $\text{CHCl}_3-d_3$ )  $\delta$ : 7.29 (s, 5H), 4.65 (t, 1H,  $J = 5.4$  Hz), 2.83 (d, 2H,  $J = 5.4$  Hz), 1.40 (bs, 2H), 0.91 (s, 9H), 0.05 (s, 3H), -0.10 (s, 3H).

**Intermediate 34**  
**6-{5-[2-(tert-Butyl-dimethyl-silanyloxy)-2-phenyl-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-nicotinamide.**



The compound is prepared according to General Procedure IV and used without further purification in the synthesis of example 219.

**Intermediate 35**  
**Benzyl-(2-methoxy-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl)-amine.**

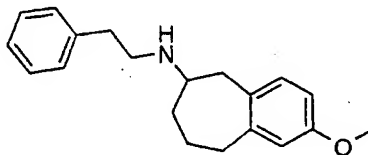


Dissolve 2-Methoxy-5,7,8,9-tetrahydro-benzocyclohepten-6-one (prepared according to JCS Perkin Trans. 1, 1992, 1475-1481, 83 mg, 0.44 mmol) in 1 mL of 19:1 methanol/acetic acid as solvent, and treat the solution with benzylamine (60  $\mu$ L, 65 mg, 0.60 mmol) and NaCNBH<sub>3</sub> (80 mg, 1.27 mmol). Agitate the reaction mixture overnight, then dilute with 25 mL dichloromethane. Wash the organic layer with 25 mL 10% aqueous potassium carbonate solution, the 25 mL brine, dry over MgSO<sub>4</sub> and evaporate to yield 103 mg product, used in subsequent chemistry without further purification; 80% crude yield.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.2-7.4: m, 5H; 7.15: m, 1H; 6.6-6.7: m, 2H; 3.8-3.9: m, 2H; 3.78: s, 3H; 2.9: m, 2H; 2.65-2.8: m, 3H; 1.5-2.05: m, 5H.

#### Intermediate 36

(2-Methoxy-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl)-phenethyl-amine.

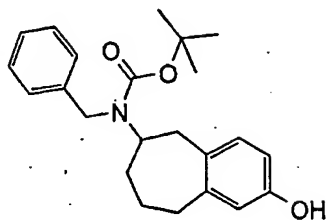


The compound is prepared analogously to Intermediate 35 using phenethylamine and was used in subsequent chemistry without further purification, 76% crude yield.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.15-7.35: m, 5H; 7.03: m, 1H; 6.03: m, 2H; 3.79: s, 3H; 2.6-3.0: m, 8H; 1.4-2.0: m, 5H.

#### Intermediate 37

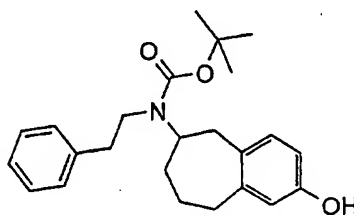
Benzyl-(2-hydroxy-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl)-carbamic acid tert-butyl ester.



Intermediate 35 (100 mg, 0.35 mmol) is dissolved in 10 mL 48% aqueous HBr and heated under reflux for 2 hours. The reaction is then cooled to room temperature and stirred overnight, then the solvent is removed under reduced pressure. The residue is dissolved in 4 mL dioxane/1 mL 1N aqueous NaOH, and BOC anhydride (100 mg, 0.46 mmol) is added and the biphasic reaction mixture is stirred for 9 days at room temperature. And additional portion of BOC anhydride (100 mg, 0.46 mmol) is added and the reaction is stirred for 2 days at room temperature. The reaction is then poured into 25 mL saturated aqueous  $\text{NH}_4\text{Cl}$ , and the aqueous phase is extracted with 25 mL  $\text{CH}_2\text{Cl}_2$ . The organic layer is dried over  $\text{MgSO}_4$  and evaporated, and the residue is purified by flash chromatography (20% Ethyl acetate/hexanes) to yield 30 mg of the desired material; 23% yield from Intermediate 35.

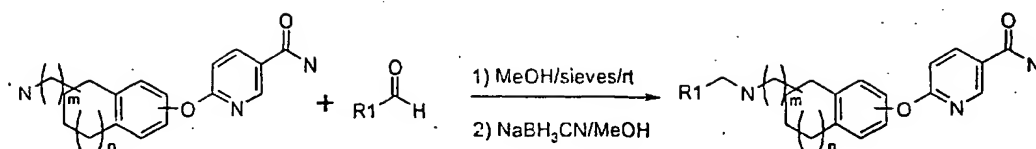
#### Intermediate 38

(2-Hydroxy-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl)-phenethyl-carbamic acid tert-butyl ester.



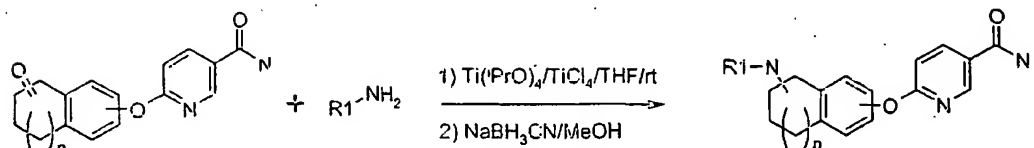
The compound is prepared analogously to Intermediate 37 starting from intermediate 36; 23% yield from Intermediate 36.

## General Procedure I



Agitate (orbital shaker) a 4 ml screw-cap vial charged with molecular sieves (ca. 200 mg), a solution of amine (0.10 M/MeOH, 100  $\mu$ mol, 1000  $\mu$ L) and a solution of aldehyde (1.0 M/MeOH, 200  $\mu$ mol, 200  $\mu$ L) at ambient temperature overnight. Treat mixture with a solution of  $NaBH_3CN$  (0.50 M/MeOH, 250  $\mu$ mol, 500  $\mu$ L) and agitate an additional three hours. Remove the molecular sieves via filtration and concentrate the filtrate under a nitrogen stream. Redissolve the filtrate in 5% AcOH/MeOH and purify on cation exchange resin (500 mg, Varian). Further purify products on reverse-phase HPLC (C18 column, 10% ACN/water (.01% TFA buffer) to 95% ACN/water over 15 minutes) and free-base on cation exchange.

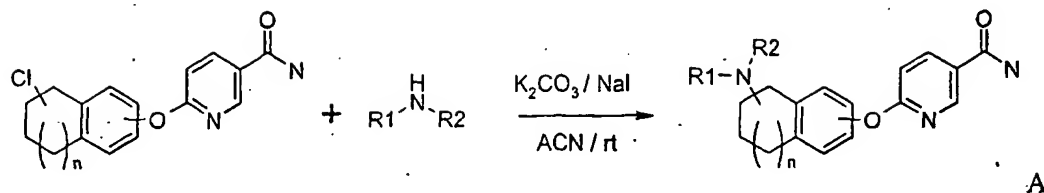
## General Procedure II



A

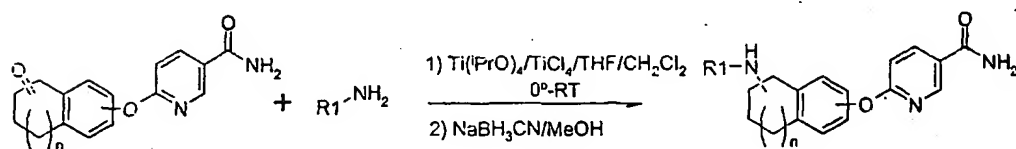
Agitate (orbital shaker) a 4 ml screw-cap vial charged with amine (120  $\mu$ mol), a solution or suspension of ketone (0.10M/THF, 100  $\mu$ mol, 1000  $\mu$ L), and solution of  $Ti(iPrO)_4$  (0.40M/THF, 200  $\mu$ mol, 500  $\mu$ L) at ambient temperature overnight. Treat the reaction with a 1.0M  $TiCl_4/DCM$  solution (200  $\mu$ mol, 200  $\mu$ L) and agitate for an additional eight hours before adding  $NaBH_3CN$  (0.50 M/MeOH, 200  $\mu$ mol, 400  $\mu$ L) and agitating overnight. Quench the reaction with 2N aq. NaOH (1 ml), agitate for one hour and spin down on centrifuge. Decant off supernate and concentrate supernate under nitrogen stream. Redissolve the filtrate in 5% AcOH/MeOH and purify on cation exchange resin (500 mg, Varian). Further purify products on reverse-phase HPLC (C18 column, 10% ACN/water (.01% TFA buffer) to 95% ACN/water over 15 minutes) and free-base on cation exchange.

## General Procedure III



gitate (orbital shaker) a 4 ml screw-cap vial charged with amine (120  $\mu$ mol),  $K_2CO_3$  (34 mg, 250  $\mu$ mol), NaI (3 mg, 20  $\mu$ mol), and a suspension of crude alkyl chloride (0.05M/CAN, 100  $\mu$ mol, 2000  $\mu$ L) at ambient temperature overnight. Remove the solids via filtration and concentrate the filtrate under a nitrogen stream. Redissolve the filtrate in 5% AcOH/MeOH and purify on cation exchange resin (500 mg, Varian). Further purify products on reverse-phase HPLC (C18 column, 10% ACN/water (.01% TFA buffer) to 95% ACN/water over 15 minutes) and free-base on cation exchange.

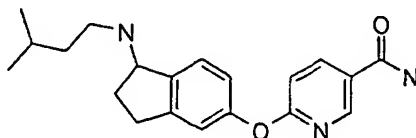
## General Procedure IV



Add  $Ti(O^iPr)_4$  (2 equiv) to a mixture of amine (1.5 equiv), ketone (1 equiv) in THF (0.04 M) is added at  $0^\circ C$  and stir the resulting reaction mixture overnight under nitrogen atmosphere at room temperature. The following day add 1.0 M solution of  $TiCl_4$  in  $CH_2Cl_2$  (2 equiv), and after 2.5 hours add  $NaCNBH_4$  (2 equiv) and stir the reaction mixture for 2 hours, then quench with saturated aqueous solution of  $NaHCO_3$  diluted with ethyl acetate. Filter off the solid and separate the organic layer, dry over anhydrous  $Na_2SO_4$  and evaporate the solvent to yield a residue which is purified by flash chromatography using EtOAc/ $CH_2Cl_2$ /2M  $NH_3$  in methanol, 0.6/0.35/0.05) to afford the title compound as a white solid.

## Example 1

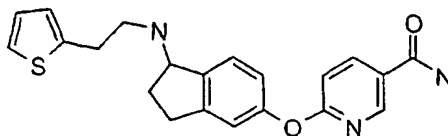
## 6-[1-(3-Methyl-butylamino)-indan-5-yloxy]-nicotinamide.



Add  $\text{Ti}(\text{iPrO})_4$  (1.70 g, 6.00 mmol) to a suspension of 6-(1-oxo-indan-5-yloxy)-nicotinamide (Intermediate 4, 805 mg, 3.00 mmol), isoamyl amine (314 mg, 3.60 mmol) and THF (10 ml) and stir overnight under a nitrogen atmosphere at ambient temperature. Treat the reaction mixture with a solution of  $\text{TiCl}_4$  (1.0M/DCM, 6.00 ml, 6.00 mmol) and stir at ambient temperature for three hours before adding  $\text{NaBH}_3\text{CN}$  (377 mg, 6.00 mmol) dissolved in MeOH (5 ml). After an additional three hours, quench the reaction with 2N aq. NaOH, making the suspension basic. Stir the suspension for one hour and filter through a filter aid to remove solids, washing them with EtOAc. Separate layers in the filtrate/wash and wash the organic layer with brine before drying ( $\text{MgSO}_4$ ) and concentrating. Purify on silica gel (5%(1N  $\text{NH}_3$ /MeOH)/45% EtOAc/DCM) to obtain 491 mg of the title compound as a light yellow solid. Mass spectrum (ion spray):  $m/z$  = 340 ( $M+1$ );  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ): 8.59 (s, 1H), 8.16 (d, 1H), 7.39 (d, 1H), 7.00 (s, 1H), 6.97-6.94 (m, 2H), 5.87 (br. s, 2H), 4.25 (t, 1H), 3.02 (m, 1H), 2.83 (m, 1H), 2.75 (t, 2H), 2.46 (m, 1H), 1.89 (m, 1H), 1.67 (m, 1H), 1.44 (m, 2H), 0.92 (d, 6H).

## Example 2

## 6-[1-(2-Thiophen-2-yl-ethylamino)-indan-5-yloxy]-nicotinamide.

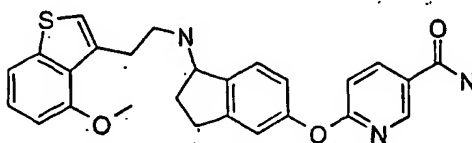


Using a method similar to Example 1, using 6-(1-oxo-indan-5-yloxy)-nicotinamide (Intermediate 4, 268 mg, 1.00 mmol), 2-thiopheneethylamine (152 mg, 1.20 mmol),  $\text{Ti}(\text{iPrO})_4$  (568 mg, 2.00 mmol),  $\text{TiCl}_4$  (1.0M/DCM, 2.00 ml, 2.00 mmol), and  $\text{NaBH}_3\text{CN}$  (125 mg, 2.00 mmol) gives the title compound (196 mg) as a white solid. Mass spectrum (ion spray):  $m/z$  = 380 ( $M+1$ );  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ): 8.58 (s, 1H), 8.15 (d, 1H), 7.35 (d, 1H), 7.16 (d, 1H), 6.99 (s, 1H), 6.96-6.93 (m, 3H), 6.86 (d, 1H), 5.81 (br. s, 2H), 4.28 (t, 1H), 3.11-2.96 (m, 5H), 2.83 (m, 1H), 2.46 (m, 1H), 1.87 (m, 1H).



## Example 3

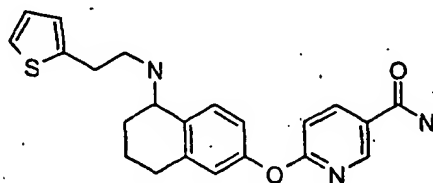
6-[1-[2-(4-Methoxy-benzo[b]thiophen-3-yl)-ethylamino]-indan-5-yloxy]-nicotinamide



Using a method similar to Example 1, using 6-(1-oxo-indan-5-yloxy)-nicotinamide (Intermediate 4, 97 mg, 0.362 mmol), 2-(4-methoxy-benzo[b]thiophen-3-yl)-ethylamine HCl salt (J. Heterocycl. Chem. (1973), 10(3), 297-305, 93 mg, 0.435 mmol), Et<sub>3</sub>N (44 mg, 0.435 mmol), Ti(<sup>i</sup>PrO)<sub>4</sub> (206 mg, 0.725 mmol), TiCl<sub>4</sub> (1.0M/DCM, 0.725 ml, 0.725 mmol), and NaBH<sub>3</sub>CN (45 mg, 0.725 mmol) gives the title compound (83 mg) as a light yellow solid. Mass spectrum (ion spray): *m/z* = 460 (M+1); <sup>1</sup>HNMR (CDCl<sub>3</sub>): 8.58 (s, 1H), 8.15 (d, 1H), 7.42 (d, 1H), 7.33 (d, 1H), 7.25 (t, 1H), 7.02 (s, 1H), 6.98 (s, 1H), 6.94-6.91 (m, 2H), 6.75 (d, 1H), 5.82 (br. s, 2H), 4.30 (t, 1H), 3.91 (s, 3H), 3.29 (t, 2H), 3.09 (m, 2H), 3.01 (m, 1H), 2.83 (m, 1H), 2.45 (m, 1H), 1.90 (m, 1H).

## Example 4

6-[5-(2-Thiophen-2-yl-ethylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide.

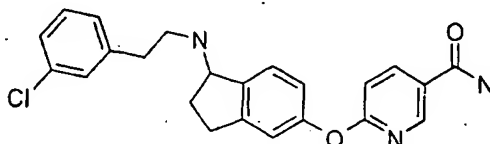


Using a method similar to Example 1, using 6-(5-oxo-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide (Intermediate 2, 546 mg, 2.00 mmol), 2-thiopheneethylamine (305 mg, 2.40 mmol), Ti(<sup>i</sup>PrO)<sub>4</sub> (1.14 g, 4.00 mmol), TiCl<sub>4</sub> (1.0M/DCM, 4.00 ml, 4.00 mmol), and NaBH<sub>3</sub>CN (251 mg, 4.00 mmol) gives the title compound (491 mg) as a light yellow solid. Mass spectrum (ion spray): *m/z* = 394 (M+1); <sup>1</sup>HNMR (CDCl<sub>3</sub>): 8.58 (s, 1H), 8.15 (d, 1H), 7.36 (d, 1H), 7.15 (d, 1H), 6.95-6.89

(m, 3H), 6.85 (m, 2H), 5.87 (br. s, 2H), 3.81 (t, 1H), 3.12-3.02 (m, 3H), 2.98 (m, 1H), 2.83-2.68 (m, 2H), 1.98-1.82 (m, 3H), 1.73 (m, 1H).

### Example 5

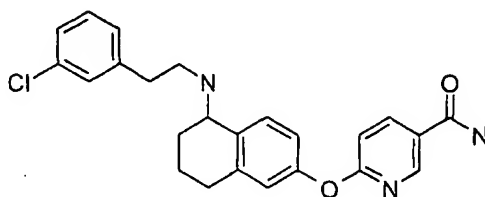
6-{1-[2-(3-Chloro-phenyl)-ethylamino]-indan-5-yloxy}-nicotinamide.



Using a method similar to Example 1, using 6-(1-oxo-indan-5-yloxy)-nicotinamide (Intermediate 4, 805 mg, 3.00 mmol), 2-(3-chlorophenyl)ethylamine (560 mg, 3.60 mmol),  $\text{Ti}(\text{tPrO})_4$  (1.70 g, 6.00 mmol),  $\text{TiCl}_4$  (1.0M/DCM, 6.00 ml, 6.00 mmol), and  $\text{NaBH}_3\text{CN}$  (377 mg, 6.00 mmol) gives the title compound (738 mg) as a white solid. Mass spectrum (ion spray):  $m/z = 408$  ( $M+1$ );  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ): 8.58 (s, 1H), 8.15 (d, 1H), 7.31 (d, 1H), 7.25-7.18 (m, 3H), 7.11 (d, 1H), 6.98-6.93 (m, 3H), 5.89 (br. s, 2H), 4.26 (t, 1H), 3.03-2.96 (m, 3H), 2.87-2.78 (m, 3H), 2.44 (m, 1H), 1.85 (m, 1H).

### Example 6

6-{5-[2-(3-Chloro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-nicotinamide.

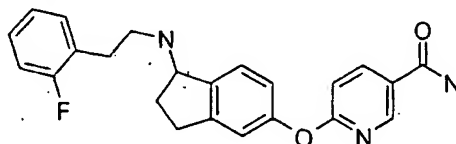


Using a method similar to Example 1, using 6-(5-oxo-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide (Intermediate 2, 846 mg, 3.00 mmol), 2-(3-chlorophenyl)ethylamine (560 mg, 3.60 mmol),  $\text{Ti}(\text{tPrO})_4$  (1.70 g, 6.00 mmol),  $\text{TiCl}_4$  (1.0M/DCM, 6.00 ml, 6.00 mmol), and  $\text{NaBH}_3\text{CN}$  (377 mg, 6.00 mmol) gives the title compound (1.16 g) as a white solid. Mass spectrum (ion spray):  $m/z = 422$  ( $M+1$ );  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ): 8.58 (s, 1H), 8.15 (d, 1H), 7.33 (d, 1H), 7.24-7.17 (m, 3H), 7.11 (d,

1H), 6.94 (d, 1H), 6.90 (d, 1H), 6.85 (s, 1H), 5.87 (br. s, 2H), 3.79 (t, 1H), 3.06-2.91 (m, 2H), 2.83-2.67 (m, 4H), 1.97-1.79 (m, 3H), 1.73 (m, 1H).

### Example 7

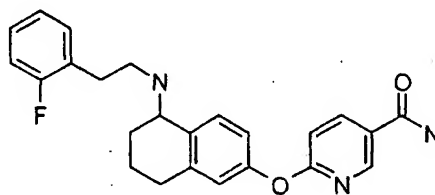
**6-{1-[2-(2-Fluoro-phenyl)-ethylamino]-indan-5-yloxy}-nicotinamide.**



Using a method similar to Example 1, using 6-(1-oxo-indan-5-yloxy)-nicotinamide (Intermediate 4, 805 mg, 3.00 mmol), 2-(2-fluorophenyl)ethylamine (501 mg, 3.60 mmol),  $\text{Ti}(\text{iPrO})_4$  (1.70 g, 6.00 mmol),  $\text{TiCl}_4$  (1.0M/DCM, 6.00 ml, 6.00 mmol), and  $\text{NaBH}_3\text{CN}$  (377 mg, 6.00 mmol) gives the title compound (398 mg) as a white solid. Mass spectrum (ion spray):  $m/z = 392$  ( $M+1$ );  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ): 8.58 (s, 1H), 8.15 (d, 1H), 7.32 (d, 1H), 7.25-7.17 (m, 2H), 7.09-7.00 (m, 2H), 6.98 (s, 1H), 6.94 (d, 2H), 5.93 (br. s, 2H), 4.28 (t, 1H), 3.04-2.95 (m, 3H), 2.92-2.87 (m, 2H), 2.83 (m, 1H), 2.45 (m, 1H), 1.85 (m, 1H).

### Example 8

**6-{5-[2-(2-Fluoro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-nicotinamide.**



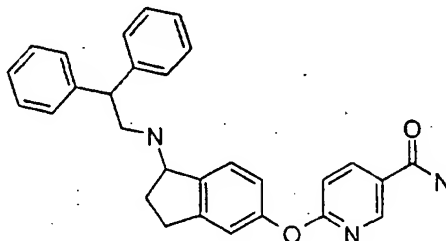
nicotinamide.

Using a method similar to Example 1, using 6-(5-oxo-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide (Intermediate 2, 846 mg, 3.00 mmol), 2-(2-fluorophenyl)ethylamine (501 mg, 3.60 mmol),  $\text{Ti}(\text{iPrO})_4$  (1.70 g, 6.00 mmol),  $\text{TiCl}_4$  (1.0M/DCM, 6.00 ml, 6.00 mmol), and  $\text{NaBH}_3\text{CN}$  (377 mg, 6.00 mmol) gives the title compound (1.01 g) as a white solid. Mass spectrum (ion spray):  $m/z = 406$  ( $M+1$ );  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ): 8.59 (s, 1H), 8.15 (d, 1H), 7.35 (d, 1H), 7.26-7.16 (m, 2H), 7.09-6.99

(m, 2H), 6.93 (d, 1H), 6.89 (d, 1H), 6.84 (s, 1H), 5.89 (br. s, 2H), 3.81 (t, 1H), 3.07-2.85 (m, 4H), 2.83-2.67 (m, 2H), 1.98-1.80 (m, 3H), 1.73 (m, 1H).

### Example 9

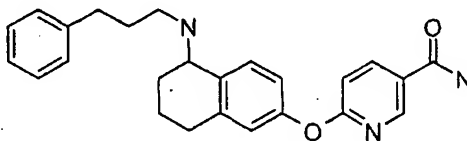
6-[1-(2,2-Diphenyl-ethylamino)-indan-5-yloxy]-nicotinamide.



Using a method similar to Example 1, using 6-(1-oxo-indan-5-yloxy)-nicotinamide (Intermediate 4, 536 mg, 2.00 mmol), 2,2-diphenylethylamine (473 mg, 2.40 mmol),  $\text{Ti}(\text{PrO})_4$  (1.14 g, 4.00 mmol),  $\text{TiCl}_4$  (1.0M/DCM, 4.00 ml, 4.00 mmol), and  $\text{NaBH}_3\text{CN}$  (251 mg, 4.00 mmol) gives the title compound (608 mg) as a white solid. Mass spectrum (ion spray):  $m/z = 450$  ( $M+1$ );  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ): 8.57 (s, 1H), 8.14 (d, 1H), 7.33-7.18 (m, 11H), 6.98-6.90 (m, 3H), 5.85 (br. s, 2H), 4.33-4.23 (m, 2H), 3.41-3.31 (m, 2H), 2.95 (m, 1H), 2.81 (m, 1H), 2.46 (m, 1H), 1.85 (m, 1H).

### Example 10

6-[5-(3-Phenyl-propylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide.

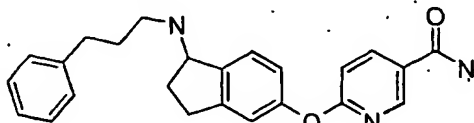


Using a method similar to Example 1, using 6-(5-oxo-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide (Intermediate 2, 564 mg, 2.00 mmol), 3-phenylpropylamine (324 mg, 2.40 mmol),  $\text{Ti}(\text{PrO})_4$  (1.14 g, 4.00 mmol),  $\text{TiCl}_4$  (1.0M/DCM, 4.00 ml, 4.00 mmol), and  $\text{NaBH}_3\text{CN}$  (251 mg, 4.00 mmol) gives the title compound (558 mg) as a light yellow solid. Mass spectrum (ion spray):  $m/z = 402$  ( $M+1$ );  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ): 8.59 (s, 1H), 8.14 (d, 1H), 7.40 (d, 1H), 7.30-7.25 (m, 2H),

7.21-7.16 (m, 3H), 6.93 (d, 1H), 6.91 (d, 1H), 6.85 (s, 1H), 5.99 (br. s, 2H), 3.74 (t, 1H), 2.84-2.64 (m, 6H), 2.00-1.79 (m, 5H), 1.72 (m, 1H).

### Example 11

#### 6-[1-(3-Phenyl-propylamino)-indan-5-yloxy]-nicotinamide.

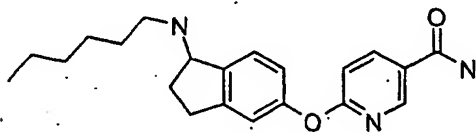


Using a method similar to Example 1, using

6-(1-oxo-indan-5-yloxy)-nicotinamide (Intermediate 4, 805 mg, 3.00 mmol), 3-phenylpropylamine (486 mg, 3.60 mmol),  $\text{Ti}(\text{PrO})_4$  (1.70 g, 6.00 mmol),  $\text{TiCl}_4$  (1.0M/DCM, 6.00 ml, 6.00 mmol), and  $\text{NaBH}_3\text{CN}$  (377 mg, 6.00 mmol) gives the title compound (681 mg) as a light yellow solid. Mass spectrum (ion spray):  $m/z = 388$ . ( $M+1$ );  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ): 8.59 (s, 1H), 8.15 (d, 1H), 7.35 (d, 1H), 7.30-7.25 (m, 2H), 7.22-7.16 (m, 3H), 6.99 (s, 1H), 6.95 (d, 1H), 5.85 (br. s, 2H), 4.23 (t, 1H), 3.00 (m, 1H), 2.83 (m, 1H), 2.78 (t, 2H), 2.70 (m, 2H), 2.43 (m, 1H), 1.87 (m, 3H).

### Example 12

#### 6-(1-Hexylamino-indan-5-yloxy)-nicotinamide

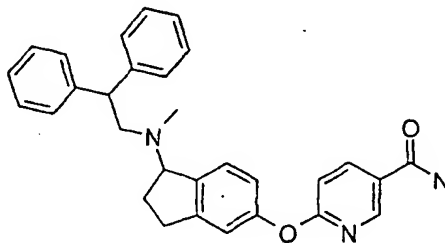


Using a method similar to Example 1, using

6-(1-oxo-indan-5-yloxy)-nicotinamide (Intermediate 4, 1.11 g, 4.14 mmol), n-hexylamine (502 mg, 4.96 mmol),  $\text{Ti}(\text{PrO})_4$  (2.35 g, 8.27 mmol),  $\text{TiCl}_4$  (1.0M/DCM, 8.27 ml, 8.27 mmol), and  $\text{NaBH}_3\text{CN}$  (520 mg, 8.27 mmol) gives the title compound (495 mg) as a tan solid. Mass spectrum (ion spray):  $m/z = 354$  ( $M+1$ );  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ): 8.59 (s, 1H), 8.16 (d, 1H), 7.38 (d, 1H), 6.99 (s, 1H), 6.96 (d, 1H), 6.94 (d, 1H), 5.92 (br. s, 2H), 4.24 (t, 1H), 3.01 (m, 1H), 2.83 (m, 1H), 2.73 (t, 2H), 2.45 (m, 1H), 1.88 (m, 1H), 1.53 (m, 3H), 1.32 (m, 5H), 0.89 (t, 3H).

## Example 13

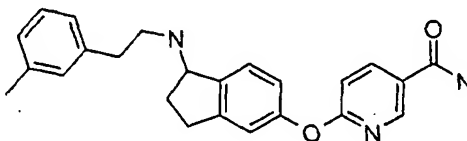
## 6-[1-(2,2-Diphenyl-ethyl)-methyl-amino]-indan-5-yloxy}-nicotinamide.



Add paraformaldehyde (57 mg) and  $\text{NaBH}_3\text{CN}$  (46 mg, 0.734 mmol) to a solution of 6-[1-(2,2-Diphenyl-ethylamino)-indan-5-yloxy]-nicotinamide (example 9, 110 mg, 0.245 mmol) in 5% AcOH/MeOH (3 ml) and stir at ambient temperature for two days. Concentrate the reaction mixture and partition remaining residue between EtOAc and 1M aq.  $\text{K}_2\text{CO}_3$ . Separate layers and wash organic with 1M aq.  $\text{K}_2\text{CO}_3$  and brine before drying ( $\text{MgSO}_4$ ) and concentrating. Purify on silica gel (5% (1N  $\text{NH}_3$ /MeOH)/45% EtOAc/DCM) to obtain 74 mg of the title compound as a white solid. Mass spectrum (ion spray):  $m/z = 464$  ( $M+1$ );  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ): 8.54 (s, 1H), 8.15 (d, 1H), 7.30-7.15 (m, 10H), 6.95-6.81 (m, 4H), 5.81 (br. s, 2H), 4.39 (t, 1H), 4.20 (t, 1H), 3.02 (d, 2H), 2.94-2.75 (m, 2H), 2.27 (s, 3H), 2.06 (m, 2H).

## Example 14

## 6-[1-(2-m-Tolyl-ethylamino)-indan-5-yloxy]-nicotinamide.

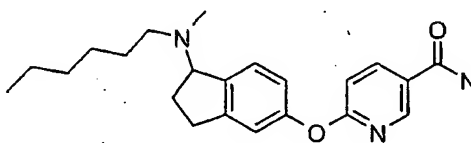


Add  $\text{Ti}(\text{iPrO})_4$  (1.70 g, 6.00 mmol) to a suspension of 6-(1-oxo-indan-5-yloxy)-nicotinamide (Intermediate 4, 805 mg, 3.00 mmol), 2-(3-methylphenyl)ethylamine (446 mg, 3.30 mmol) and THF (20 ml) and stir for six hours under a nitrogen atmosphere at ambient temperature. After cooling in an ice/water bath, treat the reaction mixture with a solution of  $\text{TiCl}_4$  (1.0M/DCM, 6.00 ml, 6.00 mmol) and stir at 0-5°C for two hours before adding  $\text{NaBH}_3\text{CN}$  (377 mg, 6.00 mmol) dissolved in MeOH (5 ml). Allow the reaction mixture to warm to ambient temperature as the cold bath warms and stir overnight.

Quench the reaction with 2N aq. NaOH, making the suspension basic. Stir the suspension for one hour and filter through a filter aid to remove solids, washing them with EtOAc. Separate layers in the filtrate/wash and wash the organic layer with brine before drying ( $\text{MgSO}_4$ ) and concentrating. Purify on silica gel (5% (1N  $\text{NH}_3$ /MeOH)/45% EtOAc/DCM) to obtain 849 mg of the title compound as a light yellow solid. Mass spectrum (ion spray):  $m/z = 388$  ( $M+1$ );  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ): 8.59 (s, 1H), 8.15 (d, 1H), 7.30 (d, 1H), 7.19 (t, 1H), 7.05-7.01 (m, 3H), 6.98 (s, 1H), 6.93 (d, 2H), 5.96 (br. s, 2H), 4.26 (t, 1H), 3.02-2.94 (m, 3H), 2.86-2.76 (m, 3H), 2.44 (m, 1H), 2.33 (s, 3H), 1.84 (m, 1H).

### Example 15

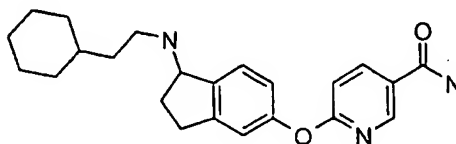
6-[1-(Hexyl-methyl-amino)-indan-5-yloxy]-nicotinamide. 2103035. AG2-A02084-114.



Using a method similar to Example 13, using 6-(1-hexylamino-indan-5-yloxy)-nicotinamide (example 12, 490 mg, 1.38 mmol), paraformaldehyde (443 mg), and  $\text{NaBH}_3\text{CN}$  (261 mg, 4.16 mmol) gives the title compound (373 mg) as a light yellow solid. Mass spectrum (ion spray):  $m/z = 368$  ( $M+1$ );  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ): 8.59 (s, 1H), 8.16 (d, 1H), 7.38 (d, 1H), 6.98-6.93 (m, 3H), 5.89 (br. s, 2H), 4.42 (t, 1H), 2.97-2.78 (m, 2H), 2.40 (m, 2H), 2.22 (s, 3H), 2.08 (m, 2H), 1.51 (m, 2H), 1.36-1.22 (m, 6H), 0.88 (t, 3H).

### Example 16

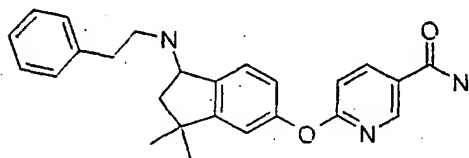
6-[1-(2-Cyclohexyl-ethylamino)-indan-5-yloxy]-nicotinamide.



Using a method similar to Example 14, using 6-(1-oxo-indan-5-yloxy)-nicotinamide (Intermediate 4, 536 mg, 2.00 mmol), 2-cyclohexylethylamine HCl ((Synthesis (1983), (5), 388-9), 393 mg, 2.40 mmol), Et<sub>3</sub>N (243 mg, 2.40 mmol), Ti(<sup>i</sup>PrO)<sub>4</sub> (1.14 g, 4.00 mmol), TiCl<sub>4</sub> (1.0M/DCM, 4.00 ml, 4.00 mmol), and NaBH<sub>3</sub>CN (251 mg, 4.00 mmol) gives the title compound (628 mg) as a yellow solid. Mass spectrum (ion spray):  $m/z = 380$  (M+1); <sup>1</sup>HNMR (CDCl<sub>3</sub>): 8.59 (s, 1H), 8.15 (d, 1H), 7.38 (d, 1H), 6.99 (s, 1H), 6.95 (d, 1H), 6.94 (d, 1H), 5.89 (br. s, 2H), 4.24 (t, 1H), 3.01 (m, 1H), 2.82 (m, 1H), 2.75 (t, 2H), 2.45 (m, 1H), 1.88 (m, 1H), 1.74-1.62 (m, 5H), 1.43 (m, 2H), 1.38-1.13 (m, 4H), 0.93 (m, 2H).

### Example 17

6-(3,3-Dimethyl-1-phenethylamino-indan-5-yloxy)-nicotinamide.

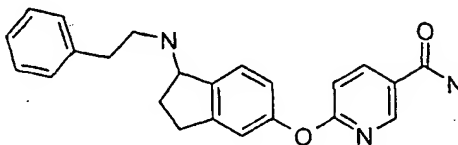


Using a method similar to Example 14, using

6-(3,3-dimethyl-1-oxo-indan-5-yloxy)-nicotinamide (Intermediate 11, 100 mg, 0.337 mmol), phenethylamine (49 mg, 0.405 mmol), Ti(<sup>i</sup>PrO)<sub>4</sub> (192 mg, 0.675 mmol), TiCl<sub>4</sub> (1.0M/DCM, 0.675 ml, 0.675 mmol), and NaBH<sub>3</sub>CN (42 mg, 0.675 mmol) gives the title compound (90 mg) as a white solid. Mass spectrum (ion spray):  $m/z = 402$  (M+1); <sup>1</sup>HNMR (CDCl<sub>3</sub>): 8.60 (s, 1H), 8.14 (d, 1H), 7.32-7.19 (m, 6H), 6.95-6.88 (m, 3H), 6.25 (br. s, 2H), 4.31 (t, 1H), 3.02 (m, 2H), 2.86 (m, 2H), 2.33 (m, 1H), 1.68 (m, 1H), 1.31 (s, 3H), 1.17 (s, 3H).

### Example 18

6-(1-Phenethylamino-indan-5-yloxy)-nicotinamide.

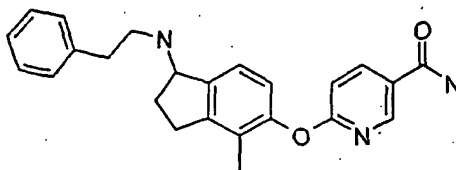




Using a method similar to Example 14, using 6-(1-oxo-indan-5-yloxy)-nicotinamide (Intermediate 4, 805 mg, 3.00 mmol), phenethylamine (436 mg, 3.60 mmol),  $\text{Ti}(\text{PrO})_4$  (1.70 g, 6.00 mmol),  $\text{TiCl}_4$  (1.0M/DCM, 6.00 ml, 6.00 mmol), and  $\text{NaBH}_3\text{CN}$  (377 mg, 6.00 mmol) gives the title compound (984 mg) as a light yellow solid. Mass spectrum (ion spray):  $m/z = 374$  ( $M+1$ );  $^1\text{HNMR}$  ( $\text{CDCl}_3$ ): 8.59 (s, 1H), 8.15 (d, 1H), 7.33-7.19 (m, 6H), 6.98 (s, 1H), 6.95-6.91 (m, 2H), 5.99 (br. s, 2H), 4.26 (t, 1H), 3.04-2.94 (m, 3H), 2.88-2.74 (m, 3H), 2.44 (m, 1H), 1.84 (m, 1H).

### Example 19

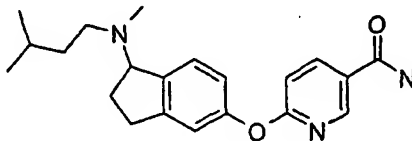
6-(4-Methyl-1-phenethylamino-indan-5-yloxy)-nicotinamide.



Using a method similar to Example 14, using 6-(4-methyl-1-oxo-indan-5-yloxy)-nicotinamide (Intermediate 12, 100 mg, 0.354 mmol), phenethylamine (52 mg, 0.425 mmol),  $\text{Ti}(\text{PrO})_4$  (201 mg, 0.708 mmol),  $\text{TiCl}_4$  (1.0M/DCM, 0.708 ml, 0.708 mmol), and  $\text{NaBH}_3\text{CN}$  (44 mg, 0.708 mmol) gives the title compound (112 mg) as a white solid. Mass spectrum (ion spray):  $m/z = 388$  ( $M+1$ );  $^1\text{HNMR}$  ( $\text{CDCl}_3$ ): 8.57 (s, 1H), 8.14 (d, 1H), 7.32-7.19 (m, 5H), 7.14 (d, 1H), 6.91-6.87 (m, 2H), 6.03 (br. s, 2H), 4.28 (t, 1H), 3.01 (t, 2H), 2.94 (m, 1H), 2.85 (m, 2H), 2.74 (m, 1H), 2.44 (m, 1H), 2.02 (s, 3H), 1.86 (m, 1H).

### Example 20

6-{1-[Methyl-(3-methyl-butyl)-amino]-indan-5-yloxy}-nicotinamide.

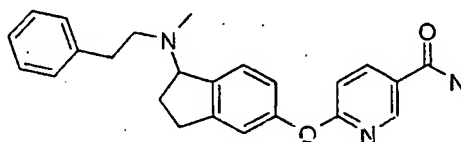


Heat a suspension of 6-(1-oxo-indan-5-yloxy)-nicotinamide (Intermediate 4, 268 mg, 1.00 mmol), methyl isoamylamine (121 mg, 1.20 mmol),  $\text{Ti}(\text{PrO})_4$  (426 mg, 1.50

mmol), and THF (0.5 ml) at 50°C overnight. Dilute the mixture with MeOH (5 ml), add  $\text{NaBH}_3\text{CN}$  (94 mg, 1.50 mmol), and stir at ambient temperature for 16 hours. Quench reaction with 2N aq. NaOH (10 ml) and stir for ca. one hour. Remove solids via filtration and wash filtercake with EtOAc. Separate layers in the filtrate/wash and wash organic layer with brine before drying ( $\text{MgSO}_4$ ) and concentrating. Redissolve the filtrate in 5% AcOH/MeOH and purify on cation exchange resin (2 g, Varian). Further purify product on reverse-phase HPLC (C18 column, 10% ACN/water (.01% TFA buffer) to 95% ACN/water over 15 minutes) and free-base with 1M aq.  $\text{K}_2\text{CO}_3$  / EtOAc to give the title compound (151 mg) as a white solid. Mass spectrum (ion spray):  $m/z = 354$  (M+1);  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ): 8.60 (s, 1H), 8.15 (d, 1H), 7.37 (d, 1H), 6.98-6.92 (m, 3H), 6.09 (br. s, 2H), 4.42 (t, 1H), 2.87 (m, 2H), 2.43 (m, 2H), 2.20 (s, 3H), 2.08 (m, 2H), 1.61 (m, 1H), 1.41 (m, 2H), 0.88 (d, 6H).

### Example 21

#### 6-[1-(Methyl-phenethyl-amino)-indan-5-yloxy]-nicotinamide.



Using a method similar to Example 13, using 6-(1-phenethylamino-indan-5-yloxy)-nicotinamide (example 18, 980 mg, 2.62 mmol), paraformaldehyde (1.03 g), and  $\text{NaBH}_3\text{CN}$  (494 mg, 7.87 mmol) gives the title compound (930 mg) as a light yellow solid. Mass spectrum (ion spray):  $m/z = 388$  (M+1);  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ): 8.59 (s, 1H), 8.16 (d, 1H), 7.30-7.17 (m, 6H), 6.97-6.91 (m, 3H), 5.79 (br. s, 2H), 4.45 (t, 1H), 2.96-2.74 (m, 4H), 2.68 (m, 2H), 2.33 (s, 3H), 2.09 (m, 2H).

### Examples 22-200

Example	IUPAC name	General Procedure	Intermed. #	Reagent	Mass (pos. ion)
22	6-(8-Pentylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide	II	1	n-pentylamine	354

23	6-(5-Pentylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide	II	2	n-pentylamine	354
24	6-(5-Pentylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide	II	3	n-pentylamine	354
25	6-(1-Pentylamino-indan-5-yloxy)-nicotinamide	II	4	n-pentylamine	340
26	6-(1-Pentylamino-indan-4-yloxy)-nicotinamide	II	5	n-pentylamine	340
27	6-(8-Benzylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide	II	1	benzylamine	374
28	6-(5-Benzylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide	II	2	benzylamine	374
29	6-(5-Benzylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide	II	3	benzylamine	374
30	6-(1-Benzylamino-indan-4-yloxy)-nicotinamide	II	5	benzylamine	360
31	6-(8-Phenethylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide	II	1	phenethylamine	388
32	6-(5-Phenethylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide	II	2	phenethylamine	388
33	6-(5-Phenethylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide	II	3	phenethylamine	388
34	6-(1-Phenethylamino-indan-4-yloxy)-nicotinamide	II	5	phenethylamine	374
35	6-{8-[2-(3-Fluoro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-nicotinamide	II	1	3-fluorophenethylamine	406
36	6-{5-[2-(3-Fluoro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-nicotinamide	II	2	3-fluorophenethylamine	406
37	6-{5-[2-(3-Fluoro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-1-yloxy}-nicotinamide	II	3	3-fluorophenethylamine	406
38	6-{3-[2-(3-Fluoro-phenyl)-ethylamino]-indan-5-yloxy}-nicotinamide	II	6	3-fluorophenethylamine	392
39	6-{1-[2-(3-Fluoro-phenyl)-ethylamino]-indan-5-yloxy}-nicotinamide	II	4	3-fluorophenethylamine	392

40	6-{1-[2-(3-Fluoro-phenyl)-ethylamino]-indan-4-yloxy}-nicotinamide	II	5	3-fluorophenethylamine	392
41	6-[8-(3-Methyl-butylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide	II	1	isoamylamine	354
42	6-[5-(3-Methyl-butylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide	II	2	isoamylamine	354
43	6-[5-(3-Methyl-butylamino)-5,6,7,8-tetrahydro-naphthalen-1-yloxy]-nicotinamide	II	3	isoamylamine	354
44	6-[8-(4-Methyl-cyclohexylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide	II	1	4-methylcyclohexylamine, cis/trans mixture	380
45	6-[5-(4-Methyl-cyclohexylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide	II	2	4-methylcyclohexylamine, cis/trans mixture	380
46	6-[5-(4-Methyl-cyclohexylamino)-5,6,7,8-tetrahydro-naphthalen-1-yloxy]-nicotinamide	II	3	4-methylcyclohexylamine, cis/trans mixture	380
47	6-[1-(4-Methyl-cyclohexylamino)-indan-5-yloxy]-nicotinamide	II	4	4-methylcyclohexylamine, cis/trans mixture	366
48	6-[1-(4-Methyl-cyclohexylamino)-indan-4-yloxy]-nicotinamide	II	5	4-methylcyclohexylamine, cis/trans mixture	366
49	6-(7-Pentylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide	II	7	n-pentylamine	354
50	6-(6-Pentylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide	II	8	n-pentylamine	354
51	6-(6-Pentylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide	II	9	n-pentylamine	354
52	6-(7-Pentylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide	II	10	n-pentylamine	354
53	6-(7-Benzylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide	II	7	benzylamine	374

54	6-(6-Benzylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide	II	8	benzylamine	374
55	6-(6-Benzylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide	II	9	benzylamine	374
56	6-(7-Benzylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide	II	10	benzylamine	374
57	6-(7-Phenethylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide	II	7	phenethylamine	387
58	6-(6-Phenethylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide	II	8	phenethylamine	387
59	6-(6-Phenethylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide	II	9	phenethylamine	387
60	6-(7-Phenethylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide	II	10	phenethylamine	387
61	6-{7-[2-(3-Fluoro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-nicotinamide	II	7	3-fluorophenethylamine	406
62	6-{6-[2-(3-Fluoro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-nicotinamide	II	8	3-fluorophenethylamine	406
63	6-{6-[2-(3-Fluoro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-1-yloxy}-nicotinamide	II	9	3-fluorophenethylamine	406
64	6-{7-[2-(3-Fluoro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-1-yloxy}-nicotinamide	II	10	3-fluorophenethylamine	406
65	6-[7-(3-Methyl-butylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide	II	7	isoamylamine	354
66	6-[6-(3-Methyl-butylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide	II	8	isoamylamine	354
67	6-[6-(3-Methyl-butylamino)-5,6,7,8-tetrahydro-naphthalen-1-yloxy]-nicotinamide	II	9	isoamylamine	354
68	6-[7-(3-Methyl-butylamino)-5,6,7,8-tetrahydro-naphthalen-1-yloxy]-	II	10	isoamylamine	354

## nicotinamide

69	6-[7-(4-Methyl- cyclohexylamino)-5,6,7,8- tetrahydro-naphthalen-2- yloxy]-nicotinamide	II	7	4- methylcyclohexylamine, cis/trans mixture	380
70	6-[6-(4-Methyl- cyclohexylamino)-5,6,7,8- tetrahydro-naphthalen-1- yloxy]-nicotinamide	II	9	4- methylcyclohexylamine, cis/trans mixture	380
71	6-[7-(4-Methyl- cyclohexylamino)-5,6,7,8- tetrahydro-naphthalen-1- yloxy]-nicotinamide	II	10	4- methylcyclohexylamine, cis/trans mixture	380
72	6-[7-(3-Phenyl-propylamino)- 5,6,7,8-tetrahydro- naphthalen-2-yloxy]- nicotinamide	II	7	3-phenylpropylamine	402
73	6-[6-(3-Phenyl-propylamino)- 5,6,7,8-tetrahydro- naphthalen-2-yloxy]- nicotinamide	II	8	3-phenylpropylamine	402
74	6-[6-(3-Phenyl-propylamino)- 5,6,7,8-tetrahydro- naphthalen-1-yloxy]- nicotinamide	II	9	3-phenylpropylamine	402
75	6-[7-(3-Phenyl-propylamino)- 5,6,7,8-tetrahydro- naphthalen-1-yloxy]- nicotinamide	II	10	3-phenylpropylamine	402
76	6-[5-(2-Methylsulfanyl- ethylamino)-5,6,7,8- tetrahydro-naphthalen-2- yloxy]-nicotinamide	II	2	2-(methylthio)- ethylamine	358
77	6-[1-(2-Methylsulfanyl- ethylamino)-indan-5-yloxy]- nicotinamide	II	4	2-(methylthio)- ethylamine	344
78	6-[5-[2-(3-Methoxy-phenyl)- ethylamino]-5,6,7,8- tetrahydro-naphthalen-2- yloxy]-nicotinamide	II	2	3- methoxyphenethylamin e	418
79	6-[1-[2-(3-Methoxy-phenyl)- ethylamino]-indan-5-yloxy]- nicotinamide	II	4	3- methoxyphenethylamin e	404
80	6-[5-(2-Dimethylamino- ethylamino)-5,6,7,8- tetrahydro-naphthalen-2- yloxy]-nicotinamide	II	2	N,N- dimethylaminoethylami ne	356
81	6-[1-(2-Dimethylamino- ethylamino)-indan-5-yloxy]- nicotinamide	II	4	N,N- dimethylaminoethylami ne	341

82	6-[5-(2-Pyrrolidin-1-yl-ethylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide	II	2	2-pyrrolidinoethylamine	381
83	6-[1-(2-Pyrrolidin-1-yl-ethylamino)-indan-5-yloxy]-nicotinamide	II	4	2-pyrrolidinoethylamine	367
84	6-[5-(2-Pyridin-2-yl-ethylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide	II	2	2-(2-aminoethyl)pyridine	389
85	6-[1-(2-Pyridin-2-yl-ethylamino)-indan-5-yloxy]-nicotinamide	II	4	2-(2-aminoethyl)pyridine	375
86	6-[5-(2-Morpholin-4-yl-ethylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide	II	2	4-(2-aminoethyl)-morpholine	397
87	6-[1-(2-Morpholin-4-yl-ethylamino)-indan-5-yloxy]-nicotinamide	II	4	4-(2-aminoethyl)-morpholine	383
88	6-[1-(1,2-Diphenyl-ethylamino)-indan-5-yloxy]-nicotinamide	II	4	1,2-diphenylethylamine	450
89	6-[5-[2-(4-Fluoro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide	II	2	4-fluoro-phenethylamine	406
90	6-[1-[2-(4-Fluoro-phenyl)-ethylamino]-indan-5-yloxy]-nicotinamide	II	4	4-fluoro-phenethylamine	390
91	6-[5-(2-Acetyl-amino-ethylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide	II	2	N-acetyl-ethylenediamine	369
92	6-[1-(2-Acetyl-amino-ethylamino)-indan-5-yloxy]-nicotinamide	II	4	N-acetyl-ethylenediamine	355
93	6-[5-[2-(5-Fluoro-1H-indol-3-yl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide	II	2	5-fluorotryptamine	445
94	6-[1-[2-(5-Fluoro-1H-indol-3-yl)-ethylamino]-indan-5-yloxy]-nicotinamide	II	4	5-fluorotryptamine	431
95	3-[6-(5-Carbamoyl-pyridin-2-yloxy)-1,2,3,4-tetrahydro-naphthalen-1-ylamino]-propionic acid isopropyl ester	II	2	4-Amino-butyric acid isopropyl ester	398

96	3-[5-(5-Carbamoyl-pyridin-2-yloxy)-indan-1-ylamino]-propionic acid isopropyl ester	II	4	4-Amino-butyric acid isopropyl ester	384
97	6-(2-Pentylamino-indan-5-yloxy)-nicotinamide	I	15	n-pentylamine	340
98	6-(2-Pentylamino-indan-4-yloxy)-nicotinamide	I	16	n-pentylamine	340
99	6-(2-Benzylamino-indan-5-yloxy)-nicotinamide	I	15	benzylamine	360
100	6-(2-Benzylamino-indan-4-yloxy)-nicotinamide	I	16	benzylamine	360
101	6-[2-(3-Phenyl-propylamino)-indan-5-yloxy]-nicotinamide	I	15	3-phenylpropylamine	388
102	6-[2-(3-Phenyl-propylamino)-indan-4-yloxy]-nicotinamide	I	16	3-phenylpropylamine	388
103	6-[2-(3-Methyl-butylamino)-indan-5-yloxy]-nicotinamide	I	15	isoamylamine	340
104	6-[2-(3-Methyl-butylamino)-indan-4-yloxy]-nicotinamide	I	16	isoamylamine	340
105	6-[2-(2-Phenyl-propylamino)-indan-5-yloxy]-nicotinamide	I	15	2-phenylpropylamine	388
106	6-[2-(2-Phenyl-propylamino)-indan-4-yloxy]-nicotinamide	I	16	2-phenylpropylamine	388
107	6-(2-Phenethylamino-indan-5-yloxy)-nicotinamide	I	15	phenethylamine	374
108	6-(2-Phenethylamino-indan-4-yloxy)-nicotinamide	I	16	phenethylamine	374
109	6-[2-[(5-Fluoro-1H-indol-3-ylmethyl)-amino]-indan-5-yloxy]-nicotinamide	I	15	5-fluorotryptamine	417
110	6-[2-[(5-Fluoro-1H-indol-3-ylmethyl)-amino]-indan-4-yloxy]-nicotinamide	I	16	5-fluorotryptamine	417
111	6-[2-(3-Dimethylamino-2,2-dimethyl-propylamino)-indan-5-yloxy]-nicotinamide	I	15	N,N,2,2-tetramethyl-1,3-propane-diamine	382
112	6-[2-(3-Dimethylamino-2,2-dimethyl-propylamino)-indan-4-yloxy]-nicotinamide	I	16	N,N,2,2-tetramethyl-1,3-propane-diamine	382
113	6-[5-[(Benzo[b]thiophen-3-ylmethyl)-amino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide	II	2	1-benzothiophen-3-ylmethylamine	430
114	6-[1-[(Benzo[b]thiophen-3-ylmethyl)-amino]-indan-5-yloxy]-nicotinamide	II	4	1-benzothiophen-3-ylmethylamine	416
115	6-[5-(2-Methoxy-ethylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide	II	2	2-methoxyethylamine	342



116	6-[1-(2-Methoxy-ethylamino)-indan-5-yloxy]-nicotinamide	II	4	2-methoxyethylamine	328
117	6-[5-[2-(3-Trifluoromethyl-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide	II	2	3-(trifluoromethyl)-phenethylamine	456
118	6-[1-[2-(3-Trifluoromethyl-phenyl)-ethylamino]-indan-5-yloxy]-nicotinamide	II	4	3-(trifluoromethyl)-phenethylamine	442
119	6-[5-(2-m-Tolyl-ethylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide	II	2	3-methyl-phenethylamine	402
120	6-[5-[2-(4-Fluoro-phenyl)-1,1-dimethyl-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide	II	2	1,1-dimethyl-2-(4-fluorophenyl)-ethylamine	299
121	6-[1-[2-(4-Fluoro-phenyl)-1,1-dimethyl-ethylamino]-indan-5-yloxy]-nicotinamide	II	4	1,1-dimethyl-2-(4-fluorophenyl)-ethylamine	285
122	6-[5-(3-Hydroxy-propylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide	II	2	3-hydroxypropylamine	343
123	6-[1-(3-Hydroxy-propylamino)-indan-5-yloxy]-nicotinamide	II	4	3-hydroxypropylamine	329
124	6-[5-(2,2,2-Trifluoro-ethylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide	II	2	2,2,2-trifluoroethylamine	299
125	6-[1-(2,2,2-Trifluoro-ethylamino)-indan-5-yloxy]-nicotinamide	II	4	2,2,2-trifluoroethylamine	285
126	6-[5-(2,2-Diphenyl-ethylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide	II	2	2,2-diphenylethylamine	464
127	6-[5-(4-Phenyl-piperidin-1-yl)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide	III	13	4-phenylpiperidine	428
128	6-[1-(4-Phenyl-piperidin-1-yl)-indan-5-yloxy]-nicotinamide	III	14	4-phenylpiperidine	414
129	6-[5-(Benzyl-methyl-amino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide	III	13	N-methylbenzylamine	388
130	6-[1-(Benzyl-methyl-amino)-indan-5-yloxy]-nicotinamide	III	14	N-methylbenzylamine	374

131	6-[5-(3,4-Dihydro-1H-isoquinolin-2-yl)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide	III	13	1,2,3,4-tetrahydro-isoquinoline	400
132	6-[1-(3,4-Dihydro-1H-isoquinolin-2-yl)-indan-5-yloxy]-nicotinamide	III	14	1,2,3,4-tetrahydro-isoquinoline	386
133	6-(5-Thiomorpholin-4-yl-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide	III	13	thio-morpholine	370
134	6-(1-Thiomorpholin-4-yl-indan-5-yloxy)-nicotinamide	III	14	thio-morpholine	356
135	2-[6-(5-Carbamoyl-pyridin-2-yloxy)-1,2,3,4-tetrahydro-naphthalen-1-yl]-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid tert-butylamide	III	13	1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid tert-butylamide	499
136	2-[6-(5-Carbamoyl-pyridin-2-yloxy)-1,2,3,4-tetrahydro-naphthalen-1-yl]-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid tert-butylamide	III	13	1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid tert-butylamide	499
137	6-[5-(5-Oxo-[1,4]diazepan-1-yl)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide	III	13	2,3,6,7-tetrahydro-(1H)-1,4-diazepin-5(4H)-one	381
138	6-[1-(5-Oxo-[1,4]diazepan-1-yl)-indan-5-yloxy]-nicotinamide	III	14	2,3,6,7-tetrahydro-(1H)-1,4-diazepin-5(4H)-one	367
139	6-[5-(Methyl-phenethyl-amino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide	III	13	N-methyl-phenethylamine	402
140	6-[1-(3-Acetylamino-pyrrolidin-1-yl)-indan-5-yloxy]-nicotinamide	III	14	3-acetamido-pyrrolidine	381
141	6-[1-(3-Phenyl-piperidin-1-yl)-indan-5-yloxy]-nicotinamide	III	14	3-phenylpiperidine	414
142	6-[1-(3-Phenyl-pyrrolidin-1-yl)-indan-5-yloxy]-nicotinamide	III	14	3-phenylpyrrolidine	400
143	6-[1-(3-Propylamino-propylamino)-indan-5-yloxy]-nicotinamide	II	4	N-propyl-1,3-propanediamine	369
144	6-[1-(3,3-Dimethyl-butylamino)-indan-5-yloxy]-nicotinamide	II	4	3,3-dimethyl-butylamine	354
145	6-(1-Decylamino-indan-5-yloxy)-nicotinamide	II	4	n-decylamine	410
146	6-[1-(2-Ethyl-hexylamino)-indan-5-yloxy]-nicotinamide	II	4	2-ethyl-hexylamine	382

147	6-[1-[(Tetrahydro-furan-2-ylmethyl)-amino]-indan-5-yloxy]-nicotinamide	II	4	tetrahydro-furfurylamine	354
148	6-(1-Cycloheptylamino-indan-5-yloxy)-nicotinamide	II	4	cycloheptylamine	366
149	6-[1-[2-(1-Methyl-pyrrolidin-2-yl)-ethylamino]-indan-5-yloxy]-nicotinamide	II	4	2-(2-aminoethyl)-1-methylpyrrolidine	381
150	6-(1-Cyclopropylamino-indan-5-yloxy)-nicotinamide	II	4	cyclopropylamine	310
151	6-[1-(1,3-Dimethyl-butylamino)-indan-5-yloxy]-nicotinamide	II	4	1,3-dimethyl-butylamine	354
152	6-(1-Cyclooctylamino-indan-5-yloxy)-nicotinamide	II	4	cyclooctylamine	380
153	6-[1-(2,3-Dimethyl-cyclohexylamino)-indan-5-yloxy]-nicotinamide	II	4	2,3-dimethylcyclohexylamine, cis/trans mixture	380
154	6-(1-Cyclobutylamino-indan-5-yloxy)-nicotinamide	II	4	cyclobutylamine	324
155	6-(1-Cyclopentylamino-indan-5-yloxy)-nicotinamide	II	4	cyclopentylamine	338
156	6-[1-(Cyclohexylmethylamino)-indan-5-yloxy]-nicotinamide	II	4	aminomethyl-cyclohexane	366
157	6-[1-[(1-Ethyl-pyrrolidin-2-ylmethyl)-amino]-indan-5-yloxy]-nicotinamide	II	4	2-aminomethyl-1-ethylpyrrolidine	381
158	6-[1-(3-Cyclohexylamino-propylamino)-indan-5-yloxy]-nicotinamide	II	4	3-Cyclohexylamino-propylamine	409
159	6-[1-(3-Methyl-cyclohexylamino)-indan-5-yloxy]-nicotinamide	II	4	3-methyl-cyclohexylamine	366
160	6-(1-Cyclohexylamino-indan-5-yloxy)-nicotinamide	II	4	cyclohexylamine	350
161	6-[1-(1-Isopropyl-2-methyl-propylamino)-indan-5-yloxy]-nicotinamide	II	4	3-amino-2,4-dimethyl-pentane	366
162	6-[1-(2-Cyclohex-1-enyl-ethylamino)-indan-5-yloxy]-nicotinamide	II	4	2-(1-cyclohexenyl)-ethylamine	378
163	6-[1-(2-Methyl-butylamino)-indan-5-yloxy]-nicotinamide	II	4	2-methylbutylamine	340
164	6-[1-(4-Hydroxy-cyclohexylamino)-indan-5-yloxy]-nicotinamide	II	4	trans-4-Hydroxy-cyclohexylamine	368
165	6-[1-(1,4-Dimethyl-pentylamino)-indan-5-yloxy]-nicotinamide	II	4	2,4-dimethylpentylamine	368

166	6-[1-(1-Cyclohexyl-ethylamino)-indan-5-yloxy]-nicotinamide	II	4	1-Cyclohexyl-ethylamine	380
167	6-[1-(3,3,5-Trimethyl-cyclohexylamino)-indan-5-yloxy]-nicotinamide	II	4	3,3,5-Trimethyl-cyclohexylamine	394
168	6-[1-(2-Carbamoyl-cyclohexylamino)-indan-5-yloxy]-nicotinamide	II	4	2-amino-cyclohexane-carboxamide	395
169	6-[1-(Cyclopropylmethyl-amino)-indan-5-yloxy]-nicotinamide	II	4	cyclopropyl-methylamine	324
170	6-[1-(3-Butoxy-propylamino)-indan-5-yloxy]-nicotinamide	II	4	3-butoxypropylamine	384
171	6-[1-(2,2,3,3,4,4,4-Heptafluoro-butylamino)-indan-5-yloxy]-nicotinamide	II	4	2,2,3,3,4,4,4-Heptafluoro-butylamine	450
172	6-[1-[3-(2-Oxo-pyrrolidin-1-yl)-propylamino]-indan-5-yloxy]-nicotinamide	II	4	1-(2-Amino-ethyl)-pyrrolidin-2-one	395
173	6-[1-(3-Azepan-1-yl-propylamino)-indan-5-yloxy]-nicotinamide	II	4	3-hexamethyleneimino-1-propylamine	409
174	6-[1-(2,2,3,3,3-Pentafluoro-propylamino)-indan-5-yloxy]-nicotinamide	II	4	2,2,3,3,3-Pentafluoro-propylamine	402
175	6-[1-[(2-Hydroxy-cyclooctylmethyl)-amino]-indan-5-yloxy]-nicotinamide	II	4	cis-2-aminomethyl-cyclooctanol	410
176	6-[1-(Bicyclohexyl-2-ylamino)-indan-5-yloxy]-nicotinamide	II	4	2-aminobicyclohexyl	434
177	6-[1-(2-Hydroxy-cyclohexylamino)-indan-5-yloxy]-nicotinamide	II	4	2-hydroxy-cyclohexylamine	368
178	6-[1-[2-(2-Methyl-cyclohexyl)-ethylamino]-indan-5-yloxy]-nicotinamide	II	4	2-(2-Methyl-cyclohexyl)-ethylamine	394
179	6-[1-[2-(4-Methyl-cyclohexyl)-ethylamino]-indan-5-yloxy]-nicotinamide	II	4	2-(4-methylcyclohexyl)-ethylamine	394
180	6-[1-(2-Cyclopentyl-ethylamino)-indan-5-yloxy]-nicotinamide	II	4	2-cyclopentyl-ethylamine	366
181	6-[1-(Phenethylamino-methyl)-indan-5-yloxy]-nicotinamide	I	17	phenethylamine	388
182	6-[8-(Phenethylamino-methyl)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide	I	19	phenethylamine	402

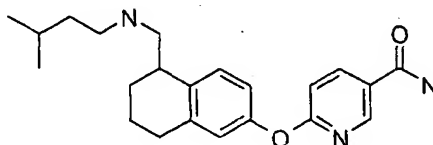
183	6-[3-(Phenethylamino-methyl)-indan-5-yloxy]-nicotinamide	1	18	phenethylamine	388
184	6-[5-(Phenethylamino-methyl)-5,6,7,8-tetrahydro-naphthalen-1-yloxy]-nicotinamide	1	20	phenethylamine	402
185	6-[1-(Benzylamino-methyl)-indan-5-yloxy]-nicotinamide	1	17	benzylamine	374
186	6-[8-(Benzylamino-methyl)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide	1	19	benzylamine	388
187	6-[3-(Benzylamino-methyl)-indan-5-yloxy]-nicotinamide	1	18	benzylamine	374
188	6-[5-(Benzylamino-methyl)-5,6,7,8-tetrahydro-naphthalen-1-yloxy]-nicotinamide	1	20	benzylamine	388
189	6-[1-[(3-Methyl-butylamino)-methyl]-indan-5-yloxy]-nicotinamide	1	17	isoamylamine	354
190	6-[8-[(3-Methyl-butylamino)-methyl]-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide	1	19	isoamylamine	368
191	6-[3-[(3-Methyl-butylamino)-methyl]-indan-5-yloxy]-nicotinamide	1	18	isoamylamine	354
192	6-[5-[(3-Methyl-butylamino)-methyl]-5,6,7,8-tetrahydro-naphthalen-1-yloxy]-nicotinamide	1	20	isoamylamine	368
193	6-[1-[(2-Cyclohexyl-ethylamino)-methyl]-indan-5-yloxy]-nicotinamide	1	17	2-cyclohexyl-ethylamine	394
194	6-[8-[(2-Cyclohexyl-ethylamino)-methyl]-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide	1	19	2-cyclohexyl-ethylamine	408
195	6-[5-[(2-Cyclohexyl-ethylamino)-methyl]-5,6,7,8-tetrahydro-naphthalen-1-yloxy]-nicotinamide	1	20	2-cyclohexyl-ethylamine	408
196	6-[1-[(Cyclohexylmethyl-amino)-methyl]-indan-5-yloxy]-nicotinamide	1	17	aminomethyl-cyclohexane	380
197	6-[8-[(Cyclohexylmethyl-amino)-methyl]-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide	1	19	aminomethyl-cyclohexane	394

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198	6-{3-[(Cyclohexylmethylamino)-methyl]-indan-5-yloxy}-nicotinamide	I	18	aminomethyl-cyclohexane	380
199	6-{5-[(Cyclohexylmethylamino)-methyl]-5,6,7,8-tetrahydro-naphthalen-1-yloxy}-nicotinamide	I	20	aminomethyl-cyclohexane	394
200	6-{1-[(2-Cyclopentylethylamino)-methyl]-indan-5-yloxy}-nicotinamide	I	17	2-cyclopentylethylamine	380

**Example 201**

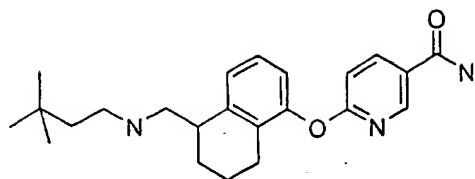
**6-{5-[(3-Methyl-butylamino)-methyl]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-nicotinamide. 2116496:**



Add isovaleraldehyde (64.5 mg, 0.750 mmol) to a solution of 6-(5-aminomethyl-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide (intermediate 21, 148 mg, 0.500 mmol) dissolved in MeOH (5 mL) and stir at ambient temperature for 1.5 hours before adding NaBH<sub>4</sub> (38 mg, 1.00 mmol). After stirring for an additional two hours, concentrate the reaction mixture and redissolved in EtOAc. Wash the EtOAc solution with 5% aq. KOH and brine before drying (MgSO<sub>4</sub>) and concentrating. Purify on silica gel (5% (1N NH<sub>3</sub>/MeOH)/DCM) to obtain 123 mg of the title compound as a white foam. Mass spectrum (ion spray): m/z = 368 (M+1); <sup>1</sup>HNMR (CDCl<sub>3</sub>): 8.59 (s, 1H), 8.15 (d, 1H), 7.25 (d, 1H), 6.94 (d, 1H), 6.89 (d, 1H), 6.85 (s, 1H), 5.82 (br. s, 2H), 2.97 (m, 1H), 2.84 (m, 2H), 2.76 (m, 2H), 2.66 (m, 2H), 1.85 (m, 3H), 1.74 (m 1H), 1.62 (m, 1H), 1.41 (m, 2H), 0.90 (d, 6H).

**Example 202**

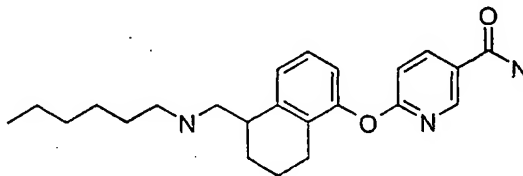
**6-{5-[(3,3-Dimethyl-butylamino)-methyl]-5,6,7,8-tetrahydro-naphthalen-1-yloxy}-nicotinamide.**



Using a method similar to Example 201, using 6-(5-aminomethyl-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide (intermediate 20, 148 mg, 0.500 mmol), 3,3-dimethylbutyraldehyde (75 mg, 0.750 mmol), and  $\text{NaBH}_4$  (38 mg, 1.00 mmol) gives the title compound (130 mg) as a white foam. Mass spectrum (ion spray):  $m/z = 382$  ( $M+1$ );  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ): 8.55 (s, 1H), 8.14 (d, 1H), 7.22-7.14 (m, 2H), 6.90 (m, 2H), 5.76 (br. s, 2H), 3.03 (m, 1H), 2.92-2.80 (m, 2H), 2.71-2.55 (m, 3H), 2.49-2.41 (m, 1H), 1.85-1.65 (m, 4H), 1.42 (t, 2H), 0.90 (s, 9H).

#### Example 203

6-(5-Hexylaminomethyl-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide.

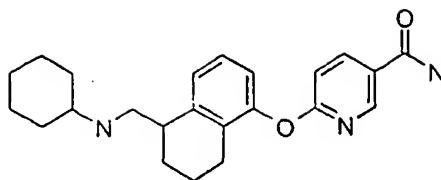


Using a method similar to Example 201, using 6-(5-aminomethyl-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide (intermediate 20, 148 mg, 0.500 mmol), hexanal (75 mg, 0.750 mmol), and  $\text{NaBH}_4$  (38 mg, 1.00 mmol) gives the title compound (110 mg) as a colorless glass. Mass spectrum (ion spray):  $m/z = 382$  ( $M+1$ );  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ): 8.57 (s, 1H), 8.15 (d, 1H), 7.21-7.14 (m, 2H), 6.90 (m, 2H), 6.05 (br. s, 2H), 3.01 (m, 1H), 2.90-2.79 (m, 2H), 2.69-2.55 (m, 3H), 2.50-2.42 (m, 1H), 1.84-1.64 (m, 4H), 1.49 (m, 2H), 1.29 (m, 6H), 0.89 (t, 3H).

#### Example 204

6-(5-Cyclohexylaminomethyl-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide.

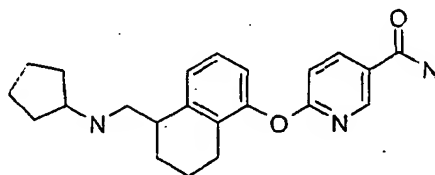
90



Add  $\text{NaBH}_3\text{CN}$  (63 mg, 1.00 mmol) to a solution of 6-(5-aminomethyl-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide (intermediate 20, 148 mg, 0.500 mmol) and cyclohexanone (98 mg, 1.00 mmol) dissolved in 5% AcOH / MeOH (5 ml) and stir at ambient temperature for 16 hours. Concentrate the reaction mixture and redissolved in EtOAc. Wash the EtOAc solution with 5% aq. KOH and brine before drying ( $\text{MgSO}_4$ ) and concentrating. Purify on silica gel (5% (1N  $\text{NH}_3$ /MeOH)/DCM) to obtain 145 mg of the title compound as a white foam. Mass spectrum (ion spray):  $m/z = 380$  ( $M+1$ );  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ): 8.56 (s, 1H), 8.15 (d, 1H), 7.22-7.14 (m, 2H), 6.90 (m, 2H), 5.79 (br. s, 2H), 2.99 (m, 1H), 2.96-2.79 (m, 2H), 2.63-2.41 (m, 3H), 1.91 (m, 2H), 1.85-1.67 (m, 6H), 1.31-1.04 (m, 6H).

### Example 205

**6-(5-Cyclopentylaminomethyl-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide.**

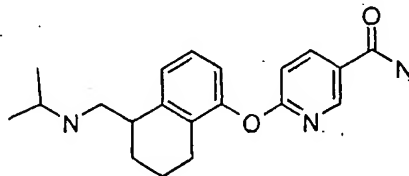


Using a method similar to Example 204, using 6-(5-aminomethyl-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide (intermediate 20, 297 mg, 1.00 mmol), cyclopentanone (168 mg, 2.00 mmol), and  $\text{NaBH}_3\text{CN}$  (125 mg, 2.00 mmol) gives the title compound (137 mg) as a white foam. Mass spectrum (ion spray):  $m/z = 366$  ( $M+1$ );  $^1\text{H}$ NMR ( $\text{CDCl}_3$ ): 8.56 (s, 1H), 8.15 (d, 1H), 7.22-7.15 (m 2H), 6.93-6.89 (m, 2H), 5.82 (br. s, 2H), 3.11 (m, 1H), 3.02 (m, 1H), 2.92-2.78 (m, 2H), 2.63-2.42 (m, 2H), 1.91-1.50 (m, 10H), 1.35 (m, 2H).



## Example 206

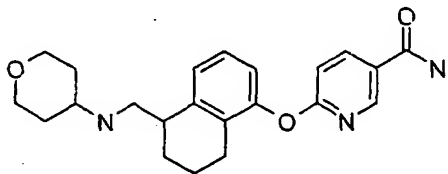
6-[5-(Isopropylamino-methyl)-5,6,7,8-tetrahydro-naphthalen-1-yloxy]-nicotinamide.



Using a method similar to Example 204, using 6-(5-aminomethyl-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide (intermediate 20, 297 mg, 1.00 mmol), acetone (116 mg, 2.00 mmol), and NaBH<sub>3</sub>CN (125 mg, 2.00 mmol) gives the title compound (139 mg) as a white foam. Mass spectrum (ion spray):  $m/z$  = 340 (M+1); <sup>1</sup>HNMR (CDCl<sub>3</sub>): 8.57 (s, 1H), 8.13 (d, 1H), 7.21-7.13 (m, 2H), 6.90-6.87 (m, 2H), 6.27 (br. s, 2H), 2.97 (m, 1H), 2.91-2.75 (m, 3H), 2.62-2.41 (m, 2H), 1.83-1.63 (m, 4H), 1.07 (d, 6H).

## Example 207

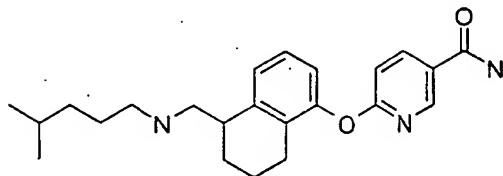
6-[5-[(Tetrahydro-pyran-4-ylamino)-methyl]-5,6,7,8-tetrahydro-naphthalen-1-yloxy]-nicotinamide.



Using a method similar to Example 204, using 6-(5-aminomethyl-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide (intermediate 20, 238 mg, 0.800 mmol), tetrahydro-4H-pyran-4-one (160 mg, 1.60 mmol), and NaBH<sub>3</sub>CN (100 mg, 1.60 mmol) gives the title compound (138 mg) as a white foam. Mass spectrum (ion spray):  $m/z$  = 382 (M+1); <sup>1</sup>HNMR (CDCl<sub>3</sub>): 8.57 (s, 1H), 8.16 (d, 1H), 7.23-7.16 (m, 2H), 6.94-6.90 (m, 2H), 5.86 (br. s, 2H), 4.00 (d, 2H), 3.40 (t, 2H), 3.15-2.78 (m, 3H), 2.65-2.41 (m, 2H), 1.97-1.46 (m, 9H).

## Example 208

6-{5-[4-Methyl-pentylamino)-methyl]-5,6,7,8-tetrahydro-naphthalen-1-yloxy}-nicotinamide.



Add NaH (60% oil suspension, 30 mg, 0.750 mmol) to a solution of [5-(5-cyano-pyridin-2-yloxy)-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-carbamic acid tert-butyl ester (Intermediate 22, 189 mg, 0.500 mmol) and DMF (5 ml) stirring at ambient temperature under nitrogen. After 20 minutes, add 1-bromo-4-methylpentane (247 mg, 1.50 mmol) and heat the mixture at 60°C overnight. After cooling, pour the mixture into water and extract with EtOAc (2x). Wash the extract with water and brine before drying ((MgSO<sub>4</sub>) and concentrating. Purify on silica gel (20% EtOAc / Hexane) to obtain 111 mg of [5-(5-cyano-pyridin-2-yloxy)-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-(4-methyl-pentyl)-carbamic acid tert-butyl ester as a colorless glass.

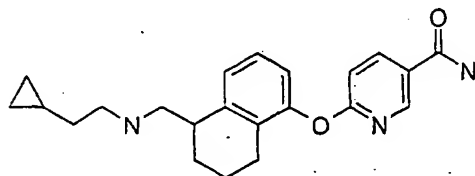
Add 30% aq. H<sub>2</sub>O<sub>2</sub> (239  $\mu$ L) to a suspension of [5-(5-cyano-pyridin-2-yloxy)-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-(4-methyl-pentyl)-carbamic acid tert-butyl ester (111 mg, 0.239 mmol), K<sub>2</sub>CO<sub>3</sub> (16 mg, 0.120 mmol) and DMSO (3 ml) stirring in an ice / water bath. After 1.5 hours, pour the reaction mixture into water and extract with EtOAc. Wash the extract with water and brine before drying (MgSO<sub>4</sub>) and concentrating to give [5-(5-Carbamoyl-pyridin-2-yloxy)-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-(4-methyl-pentyl)-carbamic acid tert-butyl ester (114 mg) as a white foam. Use this material without further purification.

Add TFA (540 mg, 4.73 mmol) to a solution of [5-(5-Carbamoyl-pyridin-2-yloxy)-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-(4-methyl-pentyl)-carbamic acid tert-butyl ester (114 mg, 0.236 mmol) and DCM (3 ml) stirring under nitrogen at ambient temperature. After 18 hours, concentrate the mixture, redissolve in EtOAc and wash with 1M aq. K<sub>2</sub>CO<sub>3</sub>, water, and brine. Dry (MgSO<sub>4</sub>), concentrate, and purify on silica gel (5% (1N NH<sub>3</sub>/MeOH)/DCM) to obtain the title compound (80 mg) as an off-white solid. Mass spectrum (ion spray): m/z = 382 (M+1); <sup>1</sup>HNMR (CDCl<sub>3</sub>): 8.56 (s, 1H), 8.15 (d,

1H), 7.21-7.13 (m, 2H), 6.90 (m, 2H), 6.04 (br. s, 2H), 3.01 (m, 1H), 2.90-2.79 (m, 2H), 2.68-2.55 (m, 3H), 2.49-2.41 (m, 1H), 1.84-1.64 (m, 4H), 1.57-1.46 (m, 3H), 1.19 (m, 2H), 0.87 (d, 6H).

### Example 209

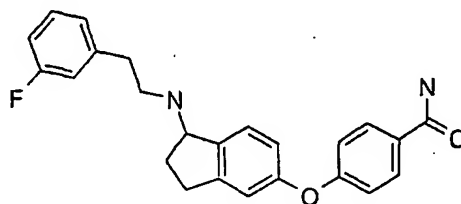
6-{5-[(2-Cyclopropyl-ethylamino)-methyl]-5,6,7,8-tetrahydro-naphthalen-1-yloxy}-nicotinamide.



Using a method similar to Example 208, using [5-(5-cyano-pyridin-2-yloxy)-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl]-carbamic acid tert-butyl ester (Intermediate 22, 379 mg, 1.00 mmol), toluene-4-sulfonic acid 2-cyclopropyl-ethyl ester (Tetrahedron (1986), 42(4), 1093-108, 721 mg, 3.00 mmol), and NaH (60% oil suspension, 80 mg, 2.00 mmol) gives the title compound (135 mg) as a white foam. Mass spectrum (ion spray):  $m/z = 366$  ( $M+1$ );  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ): 8.56 (s, 1H), 8.15 (d, 1H), 7.23-7.15 (m, 2H), 6.92 (m, 2H), 5.77 (br. s, 2H), 3.05 (m, 1H), 2.94-2.74 (m, 4H), 2.64-2.43 (m, 2H), 1.87-1.58 (m, 4H), 1.44 (m, 2H), 0.68 (m, 1H), 0.44 (m, 2H), 0.07 (m, 2H).

### Example 210

4-{1-[2-(3-Fluoro-phenyl)-ethylamino]-indan-5-yloxy}-benzamide.

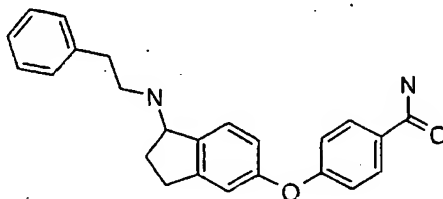


In a round bottom flask, combine 4-(1-Oxo-indan-5-yloxy)-benzamide (Intermediate 24, 45.0mg, 0.17mmol), m-Fluorophenethylamine (33uL, 0.25mmol), THF (5mL), and  $\text{Ti}(\text{O}i\text{Pr})_4$  (0.1mL, 0.27mmol) at  $0^\circ\text{C}$  under nitrogen atmosphere. Stir the reaction for 3 hours then add  $\text{TiCl}_4$  (0.3mL, 0.27mmol) at  $0^\circ\text{C}$ . For the next 2 hours,

warm the reaction to room temperature and then add  $\text{BH}_3\text{SMe}_2$  (0.09mL, 0.17mmol). Stir the reaction at room temperature for 12 hours, then add 1N NaOH (aq) and stir for 2 hours. Centrifuge and decant the reaction into a separatory funnel and wash the organic phase with water and dry over  $\text{Na}_2\text{SO}_4$ . Concentrate the reaction under reduced pressure and purify using reverse phase chromatography (5% to 95% 0.001% TFA buffer in acetonitrile/water) to afford 3.8mg, 0.01mmol (6% yield) of the title compound:

#### Example 211

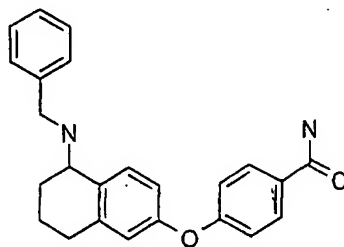
##### 4-(1-Phenethylamino-indan-5-yloxy)-benzamide.



Using a method similar to Example 210, using Phenethylamine (32uL, 0.25mmol) gives 4.0 mg (6% yield) of the title compound:

#### Example 212

##### 4-(5-Benzylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-benzamide.

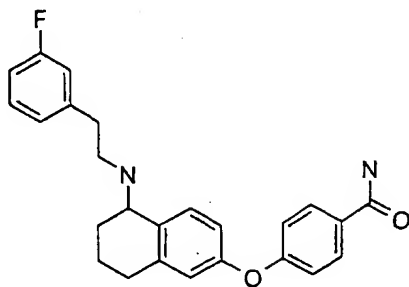


Combine 4-(5-Oxo-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-benzamide (Intermediate 26, 120.0 mg, 0.43 mmol), Benzylamine (70 uL, 0.64 mmol), THF (3 mL), and  $\text{Ti}(\text{O}i\text{Pr})_4$  (0.2 mL, 0.68 mmol) at 0°C. Stir the reaction for 12 hours allowing it to come to room temperature and then add  $\text{TiCl}_4$  (0.7 mL, 0.68 mmol) at 0°C. After reaction stirs for 3 hours, add  $\text{BH}_3\text{SMe}_2$  at room temperature. After the reaction stirs for 72 hours, add 1N NaOH aq (6 mL) at room temperature. Upon addition, a precipitate forms.

Allow the reaction to stir for an additions 12 hours, centrifuge, and decant off aqueous and organic layers. Separate the organic layer and concentrate. Add the organic mixture to a 2g SCX column, wash with MeOH, and elute with 1N NH<sub>3</sub> MeOH. Purify using reverse-phase chromatography (5% to 95% 0.001% TFA buffer in acetonitrile/water) to afford 19.4 mg, 0.05 mmol (12% yield) of the title compound: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>); 1.7-1.8 (2H, m), 1.9-2.1 (3H, m), 2.6-2.9 (2H, m), 3.8-4.0 (3H, m), 6.7-6.9 (2H, m), 6.9-7.0 (2H, m), 7.2-7.5 (6H, m), 7.7-7.9 (2H,m); MS *m/z* 284 (M of SM+3).

### Example 213

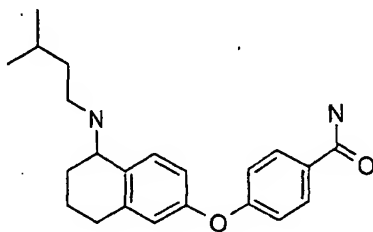
4-{5-[2-(3-Fluoro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-benzamide.



Using a method similar to Example 212, using *m*-Fluorophenethylamine (84  $\mu$ L, 0.64 mmol) gives 26.5 mg (15% yield) of the title compound : <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>); 1.6-1.8 (1H, m), 1.8-2.0 (3H, m), 2.5-3.0 (6H, m), 3.7-3.8 (1H, m), 5.6-6.1 (2H, br d), 6.6-7.0 (7H, m), 7.1-7.3 (2H, m), 7.7-7.9 (2H, m); MS *m/z* 250 (M of SM+3).

### Example 214

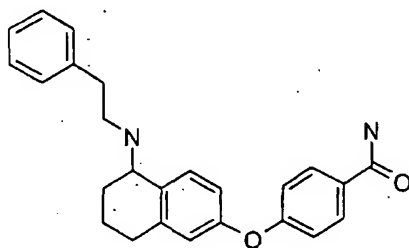
4-[5-(3-Methyl-butylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-benzamide.



Using a method similar to Example 212, using Isoamylamine (74  $\mu$ L, 0.64 mmol) gives 45.0 mg (30% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 0.8-1.0 (6H, m), 1.3-1.5 (2H, m), 1.5-1.8 (2H, m), 1.8-2.0 (3H, m), 2.6-2.8 (4H, m), 3.7-3.8 (1H, m), 5.8-6.2 (2H, br s), 6.7-6.9 (2H, m), 6.9-7.0 (2H, m), 7.2-7.4 (1H, m), 7.7-7.8 (2H, m); MS  $m/z$  353 (M+1) and 284 (M of SM+3).

### Example 215

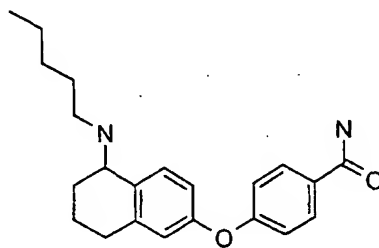
4-(5-Phenethylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-benzamide.



Using a method similar to Example 212, using Phenethylamine (80  $\mu$ L, 0.64 mmol) gives 21.7 mg (13% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 1.5-2.2 (5H, m), 2.5-3.1 (6H, m), 3.2-3.4 (1H, m), 3.7-3.9 (1H, m), 6.7-6.9 (2H, m), 6.9-7.1 (2H, m), 7.1-7.4 (6H, m), 7.7-7.9 (2H, m); MS  $m/z$  284 (M of SM+3).

### Example 216

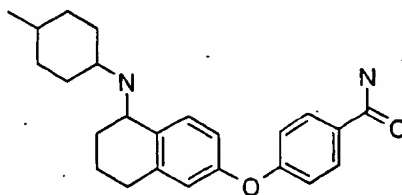
4-(5-Pentylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-benzamide.



Using a method similar to Example 212, using Pentylamine (75  $\mu$ L, 0.64 mmol) gives 73.6 mg (49% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 0.8-1.0 (3H, m), 1.2-1.4 (4H, m), 1.4-1.6 (2H, m), 1.6-1.8 (1H, m), 1.8-2.0 (3H, m), 2.6-2.9 (4H, m), 3.7-3.8 (1H, m), 6.1-6.4 (2H, br s), 6.7-6.9 (2H, m), 6.9-7.1 (2H, m), 7.2-7.4 (1H, m), 7.7-7.9 (2H, m); MS  $m/z$  284 (M of SM+3).

**Example 217**

**4-[5-(4-Methyl-cyclohexylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-benzamide.**

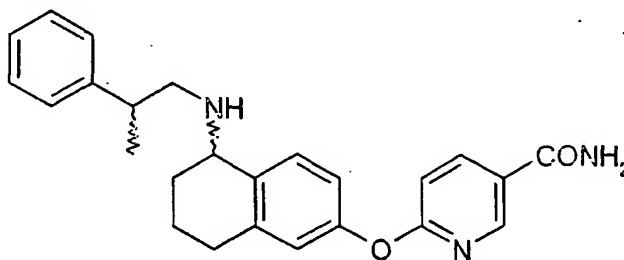


Using a method similar to Example 212, using

4-Methylcyclohexylamine (85 uL, 0.64 mmol) gives 95.0 mg (58% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); .9-1.2 (6H, m), 1.3-1.6 (4H, m), 1.6-2.0 (7H, m), 2.6-3.0 (3H, m), 3.8-3.9 (1H, m), 6.2-6.4 (2H, br s), 6.7-7.0 (4H, m), 7.3-7.4 (1H, m), 7.7-7.9 (2H, m); MS  $m/z$  284 (M of SM+3).

**Example 218**

**6-[5-(2-Phenyl-propylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide.**



Prepared according to General Procedure IV using intermediate 2 and 2-methyl-phenethylamine, to afford a 50% yield.

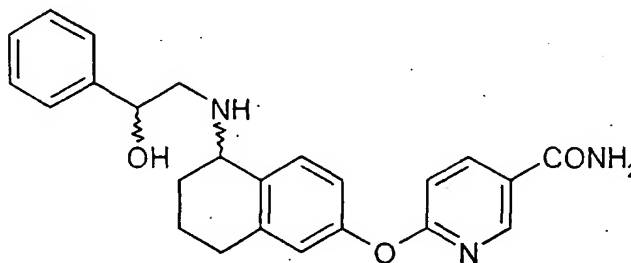
$^1\text{H}$  NMR ( $\text{MeOD}-d_4$ )  $\delta$ : 8.56 (d, 1H,  $J = 2.4$  Hz), 8.17 (dd, 1H,  $J = 8.6, 2.4$  Hz), 7.40-7.10 (m, 5H), 7.02-6.75 (m, 4H), 3.80-3.90 (m, 1H), 3.00-2.90 (m, 3H), 2.70-2.60 (m, 2H), 1.95-1.60 (m, 4H), 1.30 (m, 4H).

$^{13}\text{C}$  NMR ( $\text{MeOD}-d_4$ )  $\delta$ : 167.2, 164.8, 164.7, 151.2, 151.1, 146.4, 143.9, 143.8, 138.5, 138.4, 138.3, 134.3, 134.2, 128.7, 128.4, 127.4, 126.0, 125.9, 125.3, 123.6, 120.1, 119.9, 117.4, 117.3, 109.3, 54.1, 53.0, 52.8, 51.5, 38.9, 38.5, 28.0, 27.9, 26.6, 26.2, 18.4, 18.3, 17.6, 17.3.

MS (Electrospray): 402.2 ( $M^+ + 1$ ).

### Example 219

6-[5-(2-Hydroxy-2-phenyl-ethylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide.



To a solution of the silyl derivative (Intermediate 34) in THF a solution 1M of tetrabutylammonium fluoride is added. The resulting solution is stirred overnight. Water and ethyl acetate is added. The aqueous layer is extracted with additional ethyl acetate. The combined organic phase was dried and evaporated to yield a crude which was purified by column chromatography.

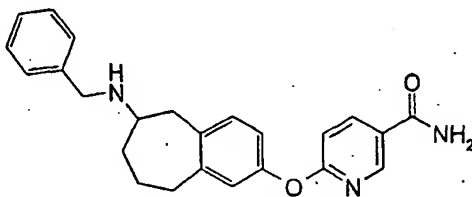
98% Yield.

$^1\text{H}$  NMR ( $\text{MeOD}-d_4$ )  $\delta$ : 8.56 (d, 1H,  $J = 2.4$  Hz), 8.17 (dd, 1H,  $J = 8.5, 2.4$  Hz), 7.55-7.25 (m, 6H), 7.02-6.80 (m, 3H), 4.00-3.80 (m, 1H), 3.00-2.60 (m, 4H), 2.00-1.60 (m, 6H).

$^{13}\text{C}$  NMR ( $\text{MeOD}-d_4$ )  $\delta$ : 168.1, 165.7, 152.2, 147.3, 143.2, 139.5, 139.3, 135.1, 129.7, 127.9, 127.1, 125.6, 124.5, 121.0, 120.9, 118.4, 110.3, 72.6, 71.8, 54.9, 54.4, 53.9, 53.5, 28.9, 27.7, 27.5, 18.4, 18.2.

MS (Electrospray): 404.2 ( $M^+ + 1$ ).

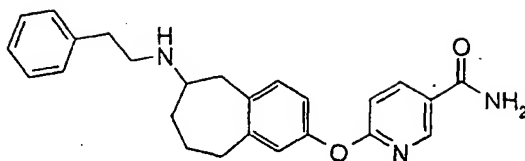


**Example 220****6-(6-Benzylamino-6,7,8,9-tetrahydro-5H-benzocyclohepten-2-yloxy)-nicotinamide.**

A solution of Intermediate 37 (30 mg, 0.08 mmol) in DMSO (0.5 mL) is treated with  $K_2CO_3$  (15 mg, 0.11 mmol) and 6-chloronicotinamide (13 mg, 0.08 mmol). The reaction mixture is heated to 100°C for 6 hours, then cooled to room temperature and poured into 25 mL  $CH_2Cl_2$ . The organics are washed with 25 mL water, 25 mL brine, then dried over  $MgSO_4$  and evaporated to give 30 mg crude material. This material is partially purified by flash chromatography using 2:1 ethyl acetate/hexanes as solvent to give 8 mg of product contaminated with 6-chloronicotinamide. The product was dissolved in 1 mL  $CH_2Cl_2$  and treated with 20  $\mu$ L of trifluoroacetic acid. After 2 hours, an additional 20  $\mu$ L of trifluoroacetic acid was added and the reaction was stirred overnight. The reaction mixture was then diluted with methanol and poured onto a 500 mg strong cation exchange column. The column was washed with methanol, and the product was eluted with 2N ammonia/methanol. Evaporation of the eluent gave 4.5 mg final product, or 14% yield from intermediate 37.

**Example 221****6-(6-Phenethylamino-6,7,8,9-tetrahydro-5H-benzocyclohepten-2-yloxy)-**

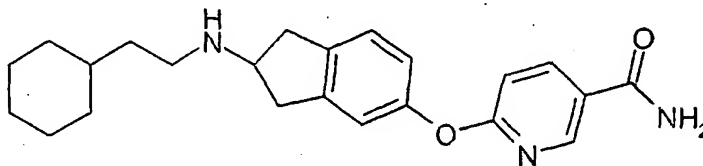
nicotinamide.



The compound is prepared analogously to example 220 starting from intermediate 38 to give 6.7 mg product, 21% yield.

#### Example 222

6-[2-(2-Cyclohexyl-ethylamino)-indan-5-yloxy]-nicotinamide.



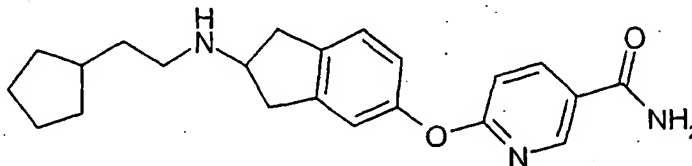
The above compound is prepared according to general Procedure V using Intermediate 15 and cyclohexane-acetaldehyde.

MS ES<sup>+</sup> (M+H)<sup>+</sup> 330.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): 8.55 (d, J = 2.44 Hz, 1H), 8.15 (dd, 1H, J = 7.8, 2.44 Hz), 7.20 (d, J = 8.3 Hz, 1H), 6.87 – 6.94 (m, 3H), 3.67 (p, J = 6.84 Hz, 1H), 3.17 (m, 2H), 2.66 – 2.83 (m, 4H), 0.89 – 1.69 (m, 13H).

#### Example 223

6-[2-(2-Cyclopentyl-ethylamino)-indan-5-yloxy]-nicotinamide.



The above compound is prepared according to General Procedure V using Intermediate 15 and cyclopentane-acetaldehyde.

MS ES<sup>+</sup> (M+H)<sup>+</sup>.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz): 8.57 (d, J = 2.44 Hz, 1H), 8.15 (dd, 1H, J = 2.44, 8.30 Hz), 7.20 (d, J = 8.3 Hz, 1H), 6.88 – 6.95 (m, 3H), 3.68 (m, 1H), 3.18 (m, 2H), 2.66 – 2.84 (m, 4H), 1.10 – 1.79 (m, 11H).

## Examples 224-246

Example	Serial #	IUPAC name	General Procedure	Intermediate #	Reagent	Mass (pos. ion)
224	2073577	6-[2-(Cyclopropylmethyl-amino)-indan-5-yloxy]-nicotinamide	V	15	cyclopropane carboxaldehyde	342
225	2073578	6-(2-Isobutylamino-indan-5-yloxy)-nicotinamide	V	15	isobutyraldehyde	326
226	2073579	6-(2-Butylamino-indan-5-yloxy)-nicotinamide	V	15	butyraldehyde	326
227	2073580	6-[2-(2-Methylbutylamino)-indan-5-yloxy]-nicotinamide	V	15	2-methylbutyraldehyde	340
228	2073581	6-[2-(3-Hydroxybutylamino)-indan-5-yloxy]-nicotinamide	V	15	3-hydroxybutyraldehyde	342

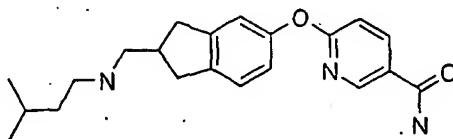
229	2073582	6-[2-(Cyclopentylmethyl-amino)-indan-5-yloxy]-nicotinamide	V	15	cyclopentane carboxaldehyde	352
230	2073583	6-[2-(2-Ethyl-butylamino)-indan-5-yloxy]-nicotinamide	V	15	2-ethylbutyraldehyde	354
231	2073584	6-[2-(2-Methyl-pentylamino)-indan-5-yloxy]-nicotinamide	V	15	2-methylpentanal	354
232	2073585	6-(2-Hexylamino-indan-5-yloxy)-nicotinamide	V	15	hexanal	354
233	2073586	6-[2-(5-Hydroxy-pentylamino)-indan-5-yloxy]-nicotinamide	V	15	5-hydroxypentanal	356
234	2073588	6-{2-[(Cyclohex-3-enylmethyl)-amino]-indan-5-yloxy}-nicotinamide	V	15	3-cyclohexene-1-carboxaldehyde	364

235	2073590	6-[2-(Cyclohexylmethyl-amino)-indan-5-yloxy]-nicotinamide	V	15	cyclohexane carboxaldehyde	366
236	2073592	6-{2-[(Bicyclo[2.2.1]hept-5-en-2-ylmethyl)-amino]-indan-5-yloxy}-nicotinamide	V	15	norbornen-5-al	376
237	2073593	6-[2-(4,4,4-Trifluoro-butylamino)-indan-5-yloxy]-nicotinamide	V	15	4,4,4-trifluorobutyraldehyde	380
238	2073594	6-[2-(3,5,5-Trimethyl-hexylamino)-indan-5-yloxy]-nicotinamide	V	15	3,5,5-trimethylhexanal	396
239	2073595	6-[2-(3-Phenyl-butylamino)-indan-5-yloxy]-nicotinamide	V	15	3-methyl-3-phenyl-propionaldehyde	402
240	2073596	6-[2-(2-Benzyloxy-ethylamino)-indan-5-yloxy]-nicotinamide	V	15	benzyloxyacetaldehyde	404

241	2073598	6-{2-[3-(5-Methyl- furan-2-yl)- butylamino]-indan- 5-yloxy}- nicotinamide	V	15	3-(5-methyl-2-furyl)- butyraldehyde	406
242	2073600	6-(2-Decylamino- indan-5-yloxy)- nicotinamide	V	15	decanal	410
243	2073601	6-{2-[3-(4- Isopropyl-phenyl)-2- methyl- propylamino]-indan- 5-yloxy}- nicotinamide	V	15	3-(4-isopropylphenyl)- isobutyraldehyde	444
244	2073603	6-[2-(3- Benzo[1,3]dioxol-5- yl-2-methyl- propylamino)-indan- 5-yloxy]- nicotinamide	V	15	2-methyl-3-(3,4- methylenedioxyphenyl)- propanal	446
245	2073605	6-[2-(2,2-Diphenyl- ethylamino)-indan- 5-yloxy]- nicotinamide	V	15	diphenyl-acetaldehyde	450
246	2076993	6-[2-(2-Cyclohexyl- ethylamino)-indan- 5-yloxy]- nicotinamide	V	15	cyclohexyl- acetaldehyde	380

## Example 247

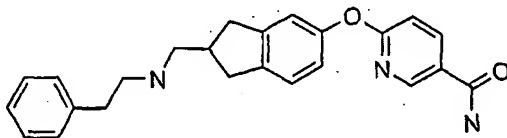
6-[2-[(3-Methyl-butylamino)-methyl]-indan-5-yloxy]-nicotinamide.



Combine 6-(2-Formyl-indan-5-yloxy)-nicotinamide (Intermediate 32, 25.3 mg, 0.09 mmol), MeOH (2.4 mL), trimethylorthoformate (1.6 mL), and isopentyl amine (9  $\mu$ L, 0.08 mmol). After the reaction stirs at room temperature under a nitrogen atmosphere for 4.5 hours, add  $\text{NaBH}_4$  (4.1 mg, 0.11 mmol), then stir at room temperature for another 12 hours. After that time, concentrate under reduced pressure then add ethyl acetate. Wash the organic phase with water, brine, and dry over  $\text{Na}_2\text{SO}_4$ . After concentration under reduced pressure the mixture, add to a 2g SCX column, wash with MeOH and elute with 1N  $\text{NH}_3$ -MeOH. After concentration, flash chromatograph using 2% 1N  $\text{NH}_3$ -MeOH, 20% THF, 38% DCM to afford 7.0 mg, 0.02 mmol (25% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz, d-Methanol); 0.9 (6H, d), 1.4-1.5 (2H, m), 1.6-1.7 (1H, m), 2.6-2.8 (6H, m), 3.1-3.2 (2H, m), 3.3-3.4 (1H, m), 6.8 (1H, d), 6.9 (1H, s), 7.1 (1H, d), 7.2 (1H, d), 8.1 (1H, d), 8.5 (1H, s); TLC 2% 1N  $\text{NH}_3$ -MeOH:20% THF:78%  $\text{CH}_2\text{Cl}_2$ :  $R_f$ =0.27.

## Example 248

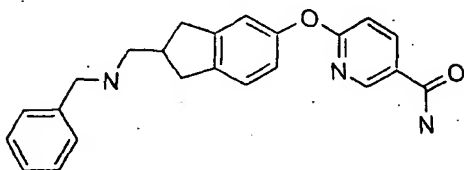
6-[2-(3-Phenethylamino-methyl)-indan-5-yloxy]-nicotinamide.



Using a method similar to Example 247, using Phenethylamine (20  $\mu$ L, 0.16 mmol) gives 17.0 mg (27% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 2.6-3.2 (12H, d), 6.8-7.0 (3H, m), 7.1-7.4 (7H, m), 7.9 (1H, d), 8.5 (1H, s); TLC 2% 1N  $\text{NH}_3$ -MeOH:20% THF:78%  $\text{CH}_2\text{Cl}_2$ :  $R_f$ =0.31.

## Example 249

6-[2-(Benzylamino)-methyl]-indan-5-yloxy]-nicotinamide.

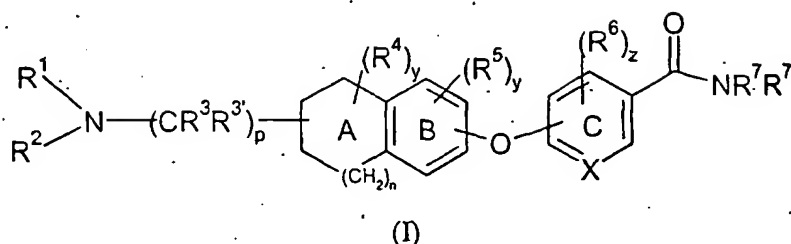


Using a method similar to Example 247, using Benzylamine (22  $\mu$ L, 0.20 mmol) gives 41.7 mg (56% yield) of the title compound:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ); 2.6-2.8 (5H, m), 3.0-3.2 (2H, m), 3.8 (2H, s), 6.8-7.0 (3H, m), 7.2-7.4 (6H, m), 7.9 (1H, d), 8.5 (1H, s); TLC 2% 1N  $\text{NH}_3$ -MeOH:20% THF:78%  $\text{CH}_2\text{Cl}_2$ :  $R_f$ =0.43



We claim:

1. A compound of the formula (I)



or a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer or a mixture thereof, wherein

X is C or N;

p is 0, 1, 2, or 3;

n is 0, 1, or 2;

$R^1$  and  $R^2$  are independently selected from hydrogen,  $C_1$ - $C_8$ alkyl,  $C_2$ - $C_8$ alkenyl,  $C_2$ - $C_8$ alkynyl,  $C_1$ - $C_{10}$ alkylaryl,  $C_4$ - $C_{10}$ alkylcycloalkane,  $C_1$ - $C_8$ alkoxyalkyl,  $(CH_2)_n C(O)OR^8$ ,  $(CH_2)_n C(O)R^8$ ,  $(CH_2)_m C(O)NR^8R^8$ , and  $(CH_2)_m NSO_2R^8$ ; wherein each of the alkyl, alkenyl, and aryl groups are optionally substituted with one to five groups independently selected from  $C_1$ - $C_8$ alkyl,  $C_2$ - $C_8$ alkenyl, phenyl,  $C_1$ - $C_8$ alkylaryl, and  $C_4$ - $C_{10}$ alkylcycloalkane, and wherein  $R^1$  and  $R^2$  may optionally combine with each other to form a 4, 5, 6, or 7-member nitrogen-containing heterocycle which nitrogen-containing heterocycle may further have substituents selected from the group consisting of oxo, amino,  $C_1$ - $C_8$ alkyl,  $C_2$ - $C_8$ alkenyl,  $C_2$ - $C_8$ alkynyl, phenyl,  $C_1$ - $C_8$ alkylaryl,  $C(O)C_1$ - $C_8$ alkyl,  $CO(O)C_1$ - $C_8$ alkyl, halo, and  $C_1$ - $C_8$ haloalkyl;

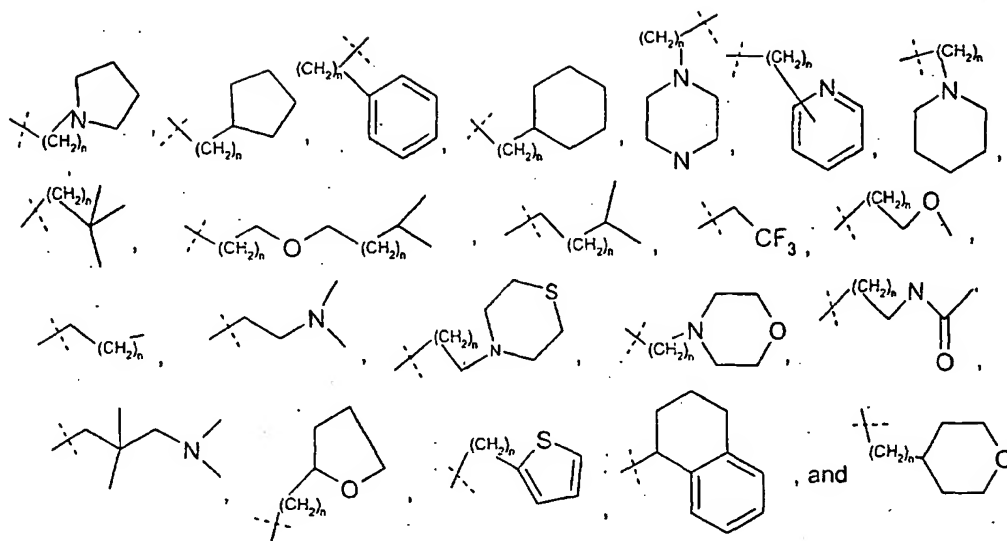
$R^3$  and  $R^{3'}$  are each independently selected from hydrogen,  $C_1$ - $C_8$ alkyl,  $C_2$ - $C_8$ alkenyl,  $C_2$ - $C_8$ alkynyl, phenyl, aryl, and  $C_1$ - $C_8$ alkylaryl;

$R^4$ ,  $R^5$ , and  $R^6$  are each independently selected from  $C_1$ - $C_8$ alkyl,  $C_2$ - $C_8$ alkenyl,  $C_2$ - $C_8$ alkynyl,  $C_1$ - $C_8$ alkoxy, halo,  $C_1$ - $C_8$ haloalkyl, phenyl, aryl,  $C_1$ - $C_8$ alkylaryl,  $(CH_2)_m NSO_2C_1$ - $C_8$ alkyl,  $(CH_2)_m NSO_2$ phenyl,  $(CH_2)_m NSO_2$ aryl,  $-C(O)C_1$ - $C_8$ alkyl, or  $-C(O)OC_1$ - $C_8$ alkyl; wherein each  $R^4$ ,  $R^5$ , and  $R^6$  is attached to its respective ring only at carbon atoms, and wherein y is 0, 1, 2, or 3; and wherein z is 0, 1, 2, or 3;

$R^7$  and  $R^{7'}$  are each independently selected from hydrogen,  $C_1$ - $C_8$ alkyl,  $C_2$ - $C_8$ alkenyl,  $C_2$ - $C_8$ alkynyl,  $C(O)C_1$ - $C_8$ alkyl, hydroxy,  $C_1$ - $C_8$ alkoxy,  $SO_2C_1$ - $C_8$ alkyl,  $SO_2C_1$ - $C_8$ alkylaryl,

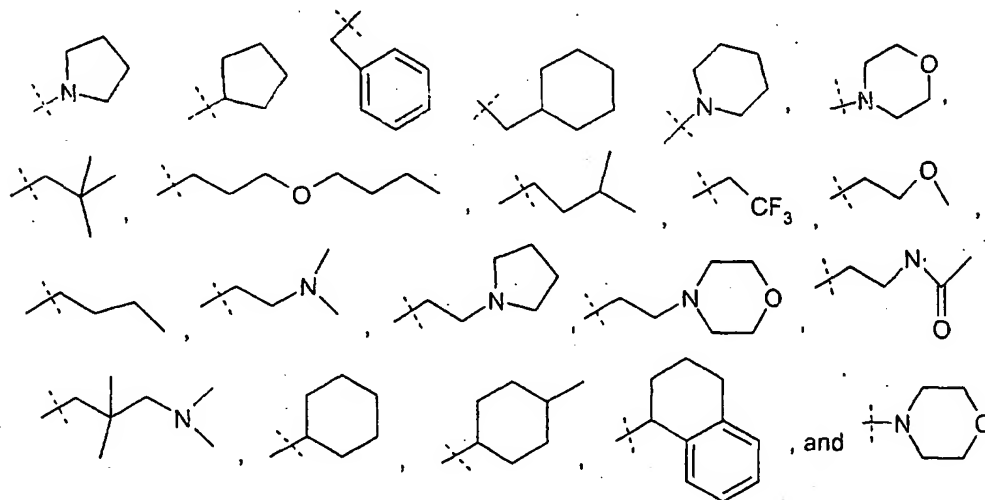
SO<sub>2</sub>C<sub>1</sub>-C<sub>8</sub>alkylheterocyclic, aryl, C<sub>1</sub>-C<sub>8</sub>alkylaryl, C<sub>3</sub>-C<sub>7</sub>cycloalkane, C<sub>1</sub>-C<sub>10</sub> alkylcycloalkane, (CH<sub>2</sub>)<sub>n</sub>C(O)OR<sup>8</sup>, (CH<sub>2</sub>)<sub>n</sub>C(O)R<sup>8</sup>, (CH<sub>2</sub>)<sub>m</sub>C(O)NR<sup>8</sup>R<sup>8</sup>, and (CH<sub>2</sub>)<sub>m</sub>NSO<sub>2</sub>R<sup>8</sup>; wherein the alkyl, alkenyl, and aryl groups are each optionally substituted with one to five groups independently selected from C<sub>1</sub>-C<sub>8</sub>alkyl, C<sub>2</sub>-C<sub>8</sub>alkenyl, phenyl, and C<sub>1</sub>-C<sub>8</sub>alkylaryl; and wherein R<sup>7</sup> and R<sup>7'</sup> may independently combine with each other, and with the nitrogen atom to which they are attached to form a 4, 5, 6, or 7-member nitrogen containing heterocycle which nitrogen containing heterocycle may further have substituents selected from the group consisting of oxo, amino, C<sub>1</sub>-C<sub>8</sub>alkyl, C<sub>2</sub>-C<sub>8</sub>alkenyl, C<sub>2</sub>-C<sub>8</sub>alkynyl, phenyl, C<sub>1</sub>-C<sub>8</sub>alkylaryl, C(O)C<sub>1</sub>-C<sub>8</sub>alkyl, CO(O)C<sub>1</sub>-C<sub>8</sub>alkyl, hydroxy, C<sub>1</sub>-C<sub>8</sub>alkoxy, halo, and haloalkyl; R<sup>8</sup> is hydrogen, C<sub>1</sub>-C<sub>8</sub>alkyl, C<sub>2</sub>-C<sub>8</sub>alkenyl, C<sub>5</sub>-C<sub>8</sub>alkylaryl, (CH<sub>2</sub>)<sub>m</sub>NSO<sub>2</sub>C<sub>1</sub>-C<sub>8</sub>alkyl, (CH<sub>2</sub>)<sub>m</sub>NSO<sub>2</sub>Phenyl, (CH<sub>2</sub>)<sub>m</sub>NSO<sub>2</sub>aryl, -C(O)C<sub>1</sub>-C<sub>8</sub>alkyl, or -C(O)OC<sub>1</sub>-C<sub>8</sub>alkyl; and m is 1 or 2.

2. The compound according to claim 1 wherein n for the A-ring is 0 or 1.
3. A compound according to Claim 1 wherein the C-ring is selected from the group consisting of phenyl and pyridine.
4. A compound according to Claim 1 wherein y is 1, or 2, and R<sup>4</sup> is independently selected from the group consisting of fluoro, chloro, methyl, ethyl, isopropyl, trifluoromethyl, phenyl, and benzyl.
5. A compound according to Claim 1 wherein z is 0, 1, or 2, and R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> are independently selected from the group consisting of fluoro, chloro, bromo, methyl, ethyl, isopropyl, trifluoromethyl, methoxy, ethoxy, phenyl, and benzyl.
6. A compound according to Claim 1 wherein R<sup>1</sup> and R<sup>2</sup> are each independently selected from the group consisting of hydrogen, methyl, ethyl, propyl, isopropyl, phenyl,



wherein  $n$  is 0, 1, or 2.

7. The compound according to Claim 1 wherein  $R^7$  and  $R^{7'}$  are each independently selected from the group consisting of Hydrogen, methyl, ethyl, propyl, pentyl, isopropyl, phenyl, benzyl,



8. A compound according to Claim 1 wherein  $R^7$  and  $R^{7'}$  are each hydrogen.

9. A compound according to Claim 1 wherein  $n$  is 1.

10. A compound according to Claim 1 wherein  $n$  is 2.

11. A compound according to Claim 1 wherein m is 1, n is 0 or 1, y is 0 or 1 and z is 0 or 1.

12. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I in association with a carrier, diluent and/or excipient.

13. A compound selected from the group consisting of:

6-(8-Pentylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,

6-(5-Pentylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,

6-(5-Pentylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide,

6-(1-Pentylamino-indan-5-yloxy)-nicotinamide,

6-(1-Pentylamino-indan-4-yloxy)-nicotinamide,

6-(8-Benzylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,

6-(5-Benzylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,

6-(5-Benzylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide,

6-(1-Benzylamino-indan-4-yloxy)-nicotinamide,

6-(8-Phenethylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,

6-(5-Phenethylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,

6-(5-Phenethylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide,

6-(1-Phenethylamino-indan-4-yloxy)-nicotinamide,

6-{8-[2-(3-Fluoro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-nicotinamide,

or a pharmaceutically acceptable salt, solvate, enantiomer or a diastereomeric mixture thereof.

14. A pharmaceutical composition comprising a compound selected from the group consisting of:

6-(8-Pentylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,

6-(5-Pentylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,

6-(5-Pentylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide,

6-(1-Pentylamino-indan-5-yloxy)-nicotinamide,

6-(1-Pentylamino-indan-4-yloxy)-nicotinamide,

6-(8-Benzylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,

6-(5-Benzylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,

6-(5-Benzylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide,

6-(1-Benzylamino-indan-4-yloxy)-nicotinamide,

6-(8-Phenethylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,

6-(5-Phenethylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,

6-(5-Phenethylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide,

6-(1-Phenethylamino-indan-4-yloxy)-nicotinamide,

6-{8-[2-(3-Fluoro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-nicotinamide,

6-{5-[2-(3-Fluoro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-  
nicotinamide,

6-{5-[2-(3-Fluoro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-1-yloxy}-  
nicotinamide,

6-{3-[2-(3-Fluoro-phenyl)-ethylamino]-indan-5-yloxy}-nicotinamide,

6-{1-[2-(3-Fluoro-phenyl)-ethylamino]-indan-5-yloxy}-nicotinamide,

6-{1-[2-(3-Fluoro-phenyl)-ethylamino]-indan-4-yloxy}-nicotinamide,

6-[8-(3-Methyl-butylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[5-(3-Methyl-butylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[5-(3-Methyl-butylamino)-5,6,7,8-tetrahydro-naphthalen-1-yloxy]-nicotinamide,

6-[8-(4-Methyl-cyclohexylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-  
nicotinamide,

6-[5-(4-Methyl-cyclohexylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-  
nicotinamide,

6-[5-(4-Methyl-cyclohexylamino)-5,6,7,8-tetrahydro-naphthalen-1-yloxy]-  
nicotinamide,

6-[1-(4-Methyl-cyclohexylamino)-indan-5-yloxy]-nicotinamide,

6-[1-(4-Methyl-cyclohexylamino)-indan-4-yloxy]-nicotinamide,

6-(7-Pentylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,

- 6-(6-Pentylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,
- 6-(6-Pentylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide,
- 6-(7-Pentylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide,
- 6-(7-Benzylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,
- 6-(6-Benzylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,
- 6-(6-Benzylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide,
- 6-(7-Benzylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide,
- 6-(7-Phenethylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,
- 6-(6-Phenethylamino-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,
- 6-(6-Phenethylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide,
- 6-(7-Phenethylamino-5,6,7,8-tetrahydro-naphthalen-1-yloxy)-nicotinamide,
- 6-{7-[2-(3-Fluoro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-  
nicotinamide,
- 6-{6-[2-(3-Fluoro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-  
nicotinamide,
- 6-{6-[2-(3-Fluoro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-1-yloxy}-  
nicotinamide,
- 6-{7-[2-(3-Fluoro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-1-yloxy}-  
nicotinamide,

6-[7-(3-Methyl-butylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[6-(3-Methyl-butylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[6-(3-Methyl-butylamino)-5,6,7,8-tetrahydro-naphthalen-1-yloxy]-nicotinamide,

6-[7-(3-Methyl-butylamino)-5,6,7,8-tetrahydro-naphthalen-1-yloxy]-nicotinamide,

6-[7-(4-Methyl-cyclohexylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-  
nicotinamide,

6-[6-(4-Methyl-cyclohexylamino)-5,6,7,8-tetrahydro-naphthalen-1-yloxy]-  
nicotinamide,

6-[7-(4-Methyl-cyclohexylamino)-5,6,7,8-tetrahydro-naphthalen-1-yloxy]-  
nicotinamide,

6-[7-(3-Phenyl-propylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[6-(3-Phenyl-propylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[6-(3-Phenyl-propylamino)-5,6,7,8-tetrahydro-naphthalen-1-yloxy]-nicotinamide,

6-[7-(3-Phenyl-propylamino)-5,6,7,8-tetrahydro-naphthalen-1-yloxy]-nicotinamide,

6-[5-(2-Methylsulfanyl-ethylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-  
nicotinamide,

6-[1-(2-Methylsulfanyl-ethylamino)-indan-5-yloxy]-nicotinamide,

6-[5-[2-(3-Methoxy-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-  
nicotinamide,

6-[1-[2-(3-Methoxy-phenyl)-ethylamino]-indan-5-yloxy]-nicotinamide,



6-[5-(2-Dimethylamino-ethylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[1-(2-Dimethylamino-ethylamino)-indan-5-yloxy]-nicotinamide,

6-[5-(2-Pyrrolidin-1-yl-ethylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[1-(2-Pyrrolidin-1-yl-ethylamino)-indan-5-yloxy]-nicotinamide,

6-[5-(2-Pyridin-2-yl-ethylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[1-(2-Pyridin-2-yl-ethylamino)-indan-5-yloxy]-nicotinamide,

6-[5-(2-Morpholin-4-yl-ethylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[1-(2-Morpholin-4-yl-ethylamino)-indan-5-yloxy]-nicotinamide,

6-[1-(1,2-Diphenyl-ethylamino)-indan-5-yloxy]-nicotinamide,

6-[5-[2-(4-Fluoro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[1-[2-(4-Fluoro-phenyl)-ethylamino]-indan-5-yloxy]-nicotinamide,

6-[5-(2-Acetyl-amino-ethylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[1-(2-Acetyl-amino-ethylamino)-indan-5-yloxy]-nicotinamide,

6-[5-[2-(5-Fluoro-1H-indol-3-yl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[1-[2-(5-Fluoro-1H-indol-3-yl)-ethylamino]-indan-5-yloxy]-nicotinamide,

3-[6-(5-Carbamoyl-pyridin-2-yloxy)-1,2,3,4-tetrahydro-naphthalen-1-ylamino]-propionic acid isopropyl ester,

3-[5-(5-Carbamoyl-pyridin-2-yloxy)-indan-1-ylamino]-propionic acid isopropyl ester,

6-(2-Pentylamino-indan-5-yloxy)-nicotinamide,

6-(2-Pentylamino-indan-4-yloxy)-nicotinamide,

6-(2-Benzylamino-indan-5-yloxy)-nicotinamide,

6-(2-Benzylamino-indan-4-yloxy)-nicotinamide,

6-[2-(3-Phenyl-propylamino)-indan-5-yloxy]-nicotinamide,

6-[2-(3-Phenyl-propylamino)-indan-4-yloxy]-nicotinamide,

6-[2-(3-Methyl-butylamino)-indan-5-yloxy]-nicotinamide,

6-[2-(3-Methyl-butylamino)-indan-4-yloxy]-nicotinamide,

6-[2-(2-Phenyl-propylamino)-indan-5-yloxy]-nicotinamide,

6-[2-(2-Phenyl-propylamino)-indan-4-yloxy]-nicotinamide,

6-(2-Phenethylamino-indan-5-yloxy)-nicotinamide,

6-(2-Phenethylamino-indan-4-yloxy)-nicotinamide,

6-{2-[(5-Fluoro-1H-indol-3-ylmethyl)-amino]-indan-5-yloxy}-nicotinamide,

6-{2-[(5-Fluoro-1H-indol-3-ylmethyl)-amino]-indan-4-yloxy}-nicotinamide,

6-[2-(3-Dimethylamino-2,2-dimethyl-propylamino)-indan-5-yloxy]-nicotinamide,

6-[2-(3-Dimethylamino-2,2-dimethyl-propylamino)-indan-4-yloxy]-nicotinamide,

6-{5-[(Benzo[b]thiophen-3-ylmethyl)-amino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-nicotinamide,

6-{1-[(Benzo[b]thiophen-3-ylmethyl)-amino]-indan-5-yloxy}-nicotinamide,

6-[5-(2-Methoxy-ethylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[1-(2-Methoxy-ethylamino)-indan-5-yloxy]-nicotinamide,

6-{5-[2-(3-Trifluoromethyl-phenyl)-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-nicotinamide,

6-{1-[2-(3-Trifluoromethyl-phenyl)-ethylamino]-indan-5-yloxy}-nicotinamide,

6-[5-(2-m-Tolyl-ethylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-{5-[2-(4-Fluoro-phenyl)-1,1-dimethyl-ethylamino]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-nicotinamide,

6-{1-[2-(4-Fluoro-phenyl)-1,1-dimethyl-ethylamino]-indan-5-yloxy}-nicotinamide,

6-[5-(3-Hydroxy-propylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[1-(3-Hydroxy-propylamino)-indan-5-yloxy]-nicotinamide,

6-[5-(2,2,2-Trifluoro-ethylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[1-(2,2,2-Trifluoro-ethylamino)-indan-5-yloxy]-nicotinamide,

6-[5-(2,2-Diphenyl-ethylamino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[5-(4-Phenyl-piperidin-1-yl)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[1-(4-Phenyl-piperidin-1-yl)-indan-5-yloxy]-nicotinamide,

6-[5-(Benzyl-methyl-amino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[1-(Benzyl-methyl-amino)-indan-5-yloxy]-nicotinamide,

6-[5-(3,4-Dihydro-1H-isoquinolin-2-yl)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[1-(3,4-Dihydro-1H-isoquinolin-2-yl)-indan-5-yloxy]-nicotinamide,

6-(5-Thiomorpholin-4-yl-5,6,7,8-tetrahydro-naphthalen-2-yloxy)-nicotinamide,

6-(1-Thiomorpholin-4-yl-indan-5-yloxy)-nicotinamide,

2-[6-(5-Carbamoyl-pyridin-2-yloxy)-1,2,3,4-tetrahydro-naphthalen-1-yl]-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid tert-butylamide,

2-[6-(5-Carbamoyl-pyridin-2-yloxy)-1,2,3,4-tetrahydro-naphthalen-1-yl]-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid tert-butylamide,

6-[5-(5-Oxo-[1,4]diazepan-1-yl)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[1-(5-Oxo-[1,4]diazepan-1-yl)-indan-5-yloxy]-nicotinamide,

6-[5-(Methyl-phenethyl-amino)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[1-(3-Acetylamino-pyrrolidin-1-yl)-indan-5-yloxy]-nicotinamide,

6-[1-(3-Phenyl-piperidin-1-yl)-indan-5-yloxy]-nicotinamide,

6-[1-(3-Phenyl-pyrrolidin-1-yl)-indan-5-yloxy]-nicotinamide,

6-[1-(3-Propylamino-propylamino)-indan-5-yloxy]-nicotinamide,

6-[1-(3,3-Dimethyl-butylamino)-indan-5-yloxy]-nicotinamide,

6-(1-Decylamino-indan-5-yloxy)-nicotinamide,

6-[1-(2-Ethyl-hexylamino)-indan-5-yloxy]-nicotinamide,

6-[1-[(Tetrahydro-furan-2-ylmethyl)-amino]-indan-5-yloxy]-nicotinamide,

6-(1-Cycloheptylamino-indan-5-yloxy)-nicotinamide,

6-{1-[2-(1-Methyl-pyrrolidin-2-yl)-ethylamino]-indan-5-yloxy}-nicotinamide,

6-(1-Cyclopropylamino-indan-5-yloxy)-nicotinamide,

6-[1-(1,3-Dimethyl-butylamino)-indan-5-yloxy]-nicotinamide,

6-(1-Cyclooctylamino-indan-5-yloxy)-nicotinamide,

6-[1-(2,3-Dimethyl-cyclohexylamino)-indan-5-yloxy]-nicotinamide,

6-(1-Cyclobutylamino-indan-5-yloxy)-nicotinamide,

6-(1-Cyclopentylamino-indan-5-yloxy)-nicotinamide,

6-[1-(Cyclohexylmethyl-amino)-indan-5-yloxy]-nicotinamide,

6-{1-[(1-Ethyl-pyrrolidin-2-ylmethyl)-amino]-indan-5-yloxy}-nicotinamide,

6-[1-(3-Cyclohexylamino-propylamino)-indan-5-yloxy]-nicotinamide,

6-[1-(3-Methyl-cyclohexylamino)-indan-5-yloxy]-nicotinamide,

6-(1-Cyclohexylamino-indan-5-yloxy)-nicotinamide,

6-[1-(1-Isopropyl-2-methyl-propylamino)-indan-5-yloxy]-nicotinamide,

6-[1-(2-Cyclohex-1-enyl-ethylamino)-indan-5-yloxy]-nicotinamide,

6-[1-(2-Methyl-butylamino)-indan-5-yloxy]-nicotinamide,

6-[1-(4-Hydroxy-cyclohexylamino)-indan-5-yloxy]-nicotinamide,

6-[1-(1,4-Dimethyl-pentylamino)-indan-5-yloxy]-nicotinamide,

6-[1-(1-Cyclohexyl-ethylamino)-indan-5-yloxy]-nicotinamide,

6-[1-(3,3,5-Trimethyl-cyclohexylamino)-indan-5-yloxy]-nicotinamide,

- 6-[1-(2-Carbamoyl-cyclohexylamino)-indan-5-yloxy]-nicotinamide,
- 6-[1-(Cyclopropylmethyl-amino)-indan-5-yloxy]-nicotinamide,
- 6-[1-(3-Butoxy-propylamino)-indan-5-yloxy]-nicotinamide,
- 6-[1-(2,2,3,3,4,4,4-Heptafluoro-butylamino)-indan-5-yloxy]-nicotinamide,
- 6-{1-[3-(2-Oxo-pyrrolidin-1-yl)-propylamino]-indan-5-yloxy}-nicotinamide,
- 6-[1-(3-Azepan-1-yl-propylamino)-indan-5-yloxy]-nicotinamide,
- 6-[1-(2,2,3,3,3-Pentafluoro-propylamino)-indan-5-yloxy]-nicotinamide,
- 6-{1-[(2-Hydroxy-cyclooctylmethyl)-amino]-indan-5-yloxy}-nicotinamide,
- 6-[1-(Bicyclohexyl-2-ylamino)-indan-5-yloxy]-nicotinamide,
- 6-[1-(2-Hydroxy-cyclohexylamino)-indan-5-yloxy]-nicotinamide,
- 6-{1-[2-(2-Methyl-cyclohexyl)-ethylamino]-indan-5-yloxy}-nicotinamide,
- 6-{1-[2-(4-Methyl-cyclohexyl)-ethylamino]-indan-5-yloxy}-nicotinamide,
- 6-[1-(2-Cyclopentyl-ethylamino)-indan-5-yloxy]-nicotinamide,
- 6-[1-(Phenethylamino-methyl)-indan-5-yloxy]-nicotinamide,
- 6-[8-(Phenethylamino-methyl)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,
- 6-[3-(Phenethylamino-methyl)-indan-5-yloxy]-nicotinamide,
- 6-[5-(Phenethylamino-methyl)-5,6,7,8-tetrahydro-naphthalen-1-yloxy]-nicotinamide,
- 6-[1-(Benzylamino-methyl)-indan-5-yloxy]-nicotinamide,

6-[8-(Benzylamino-methyl)-5,6,7,8-tetrahydro-naphthalen-2-yloxy]-nicotinamide,

6-[3-(Benzylamino-methyl)-indan-5-yloxy]-nicotinamide,

6-[5-(Benzylamino-methyl)-5,6,7,8-tetrahydro-naphthalen-1-yloxy]-nicotinamide,

6-{1-[(3-Methyl-butylamino)-methyl]-indan-5-yloxy}-nicotinamide,

6-{8-[(3-Methyl-butylamino)-methyl]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-  
nicotinamide,

6-{3-[(3-Methyl-butylamino)-methyl]-indan-5-yloxy}-nicotinamide,

6-{5-[(3-Methyl-butylamino)-methyl]-5,6,7,8-tetrahydro-naphthalen-1-yloxy}-  
nicotinamide,

6-{1-[(2-Cyclohexyl-ethylamino)-methyl]-indan-5-yloxy}-nicotinamide,

6-{8-[(2-Cyclohexyl-ethylamino)-methyl]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-  
nicotinamide,

6-{5-[(2-Cyclohexyl-ethylamino)-methyl]-5,6,7,8-tetrahydro-naphthalen-1-yloxy}-  
nicotinamide,

6-{1-[(Cyclohexylmethyl-amino)-methyl]-indan-5-yloxy}-nicotinamide,

6-{8-[(Cyclohexylmethyl-amino)-methyl]-5,6,7,8-tetrahydro-naphthalen-2-yloxy}-  
nicotinamide,

6-{3-[(Cyclohexylmethyl-amino)-methyl]-indan-5-yloxy}-nicotinamide,

6-{5-[(Cyclohexylmethyl-amino)-methyl]-5,6,7,8-tetrahydro-naphthalen-1-yloxy}-  
nicotinamide,

6-{1-[(2-Cyclopentyl-ethylamino)-methyl]-indan-5-yloxy}-nicotinamide,

and a pharmaceutically acceptable salt, solvate or enantiomer thereof.

15. A method for blocking a mu, kappa, delta or receptor combination (heterodimer) thereof in mammals comprising administering to a mammal requiring blocking of a mu, kappa, delta or receptor combination (heterodimer) thereof, a receptor blocking dose of a compound of the formula I, or a pharmaceutically acceptable salt, enantiomer, racemate, mixture of diastereomers, or solvate thereof.

16. A method of treating or preventing obesity and Related Diseases comprising administering a therapeutically effective amount of a compound of formula I to a patient in need thereof.

17. A method according to Claim 15 wherein the Related Diseases is selected from the group consisting of diabetes, diabetic complications, diabetic retinopathy, atherosclerosis, hyperlipidemia, hypertriglycemia, hyperglycemia, and hyperlipoproteinemia, irritable bowel syndrome, nausea, vomiting, depression, smoking and alcohol addiction, sexual dysfunction, substance abuse, drug overdose, addictive behavior disorders, compulsive behaviors, and stroke comprising administering a therapeutically effective amount of a compound of formula I.

18. Use of a compound of formula I in the manufacture of a medicament for the treatment and/or amelioration of the symptoms associated with obesity and Related Diseases comprising administering a therapeutically effective amount of a compound of formula I to a patient in need thereof.

19. A method of suppressing appetite in a patient in need thereof, comprising administering a therapeutically effective amount of a compound of formula I to said patient.



## INTERNATIONAL SEARCH REPORT

Int'l Application No  
PC1/US2004/003360

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D213/82 C07D409/12 C07D405/12 C07D401/12 A61K31/4427  
A61P3/04 A61P1/08 A61P17/04 A61P25/30 A61P25/24  
A61P15/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document: with indication, where appropriate, of the relevant passages	Relevant to claim No
Y	EP 0 827 746 A (LILLY CO ELI) 11 March 1998 (1998-03-11) preparation 93, p.37 page 2, line 1 - page 3, line 52; claim 1 page 78, lines 46-58	1-19
A	WO 95/35316 A (SCHILLER PETER ; ASTRA AB (SE)) 28 December 1995 (1995-12-28) page 1, lines 7-10; claim 1	1-19
A	WO 96/36620 A (SMITHKLINE BEECHAM SPA ; DONDIO GIULIO (IT); RONZONI SILVANO (IT)) 21 November 1996 (1996-11-21) page 7, paragraph 5; claims 1,7	1-19
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
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- \*O\* document referring to an oral disclosure, use, exhibition or other means
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- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search

2 July 2004

Date of mailing of the international search report

14/07/2004

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## INTERNATIONAL SEARCH REPORT

In  
Patent Application No  
PCT/US2004/003360

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99/33806 A (FITZPATRICK LOUIS J ; CARSON JOHN R (US); REITZ ALLEN B (US); CARMOSIN) 8 July 1999 (1999-07-08) page 1, line 7 - line 16; claims 1,8-14 -----	1-19
A	WO 01/46198 A (TRUSTEES OF THE UNIVERSITY OF) 28 June 2001 (2001-06-28) claim 1 -----	1-19
E	WO 2004/026305 A (PEDREGAL-TERCERO CONCEPCION ; DE LA TORRE MARTA GARCIA (ES); DIAZ BUEZ) 1 April 2004 (2004-04-01) the whole document -----	1-19

Form PCT/ISA/210 (continuation of second sheet) (January 2004)

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2004/003360

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely.  
  
Although claims 15-17 and 19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2004)

## INTERNATIONAL SEARCH REPORT

Information on patent family members

In International Application No  
PCT/US2004/003360

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0827746	A	11-03-1998	AT 215369 T	15-04-2002
			AU 4094197 A	26-03-1998
			CA 2236269 A1	12-03-1998
			DE 69711519 D1	08-05-2002
			DE 69711519 T2	31-10-2002
			EP 0827746 A1	11-03-1998
			ES 2171839 T3	16-09-2002
			ID 17182 A	04-12-1997
			JP 2002513387 T	08-05-2002
			US 6140352 A	31-10-2000
			WO 9809625 A1	12-03-1998
			US 2002165234 A1	07-11-2002
			US 6413991 B1	02-07-2002
			ZA 9707917 A	03-06-1999
WO 9535316	A	28-12-1995	AU 691630 B2	21-05-1998
			AU 2811495 A	15-01-1996
			CA 2192484 A1	28-12-1995
			FI 965116 A	19-12-1996
			JP 10501807 T	17-02-1998
			NO 965457 A	18-12-1996
			NZ 288775 A	26-02-1998
			WO 9535316 A1	28-12-1995
			US 5733881 A	31-03-1998
			ZA 9504311 A	22-01-1996
WO 9636620	A	21-11-1996	EP 0777682 A1	11-06-1997
			IT MI951020 A1	19-11-1996
			AT 213735 T	15-03-2002
			AU 5899896 A	29-11-1996
			BR 9608458 A	05-01-1999
			CA 2221380 A1	21-11-1996
			CN 1190393 A	12-08-1998
			CZ 9703652 A3	17-06-1998
			DE 69619512 D1	04-04-2002
			DE 69619512 T2	31-10-2002
WO 9636620	A	21-11-1996	WO 9636620 A1	21-11-1996
			EP 0825991 A1	04-03-1998
			ES 2171675 T3	16-09-2002
			HU 9802222 A2	28-07-1999
			JP 3205343 B2	04-09-2001
			JP 11505237 T	18-05-1999
			NO 975294 A	18-11-1997
			PL 323385 A1	30-03-1998
			TR 9701388 T1	21-03-1998
			US 5922887 A	13-07-1999
WO 9933806	A	08-07-1999	ZA 9603939 A	21-01-1997
			AU 2009799 A	19-07-1999
			CA 2316341 A1	08-07-1999
			EP 1049676 A1	08-11-2000
			JP 2001527068 T	25-12-2001
			TW 476755 B	21-02-2002
			WO 9933806 A1	08-07-1999
			ZA 9811842 A	23-06-2000
WO 0146198	A	28-06-2001	US 6284769 B1	04-09-2001
			AU 4511901 A	03-07-2001

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2004/003360

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0146198 A		WO 0146198 A2	28-06-2001
WO 2004026305 A	01-04-2004	WO 2004026305 A1	01-04-2004

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